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ORGANIC SEMINAR ABSTRACTS

1988-89, SEMESTER I

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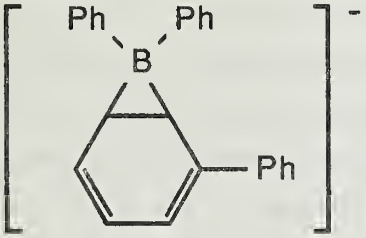
DI-π-METHANE REARRANGEMENTS OF ARYL BORATES.

Reported by Michael Kropp September 19, 1988

The di-π-methane rearrangement is one of the most thoroughly studied photochemical reactions of carbon systems.[1] Recently, the photolyses of tetraaryl- and related borates have been investigated and found to follow this same pathway formally.

The photochemical rearrangement of tetraarylborates has been the subject of numerous investigations.[2] Williams and co-workers found biphenyl was formed when sodium tetraphenylborate was photolyzed.[3] Labelling experiments showed that the coupling of the aryl groups occurs intramolecularly and that the new bond in the biaryl product is formed from the carbon atoms initially bound to boron. Further results led to the postulation of a mechanism involving a bridging boron species, arising from initial carbon-boron bond homolysis.[4]

A recent reinvestigation of the irradiation of tetraphenylborate has shown that, instead of leading to the direct formation of biphenyl and diphenylborene as was claimed[5], the initial photoproduct isolated is the bridged species **1**, postulated to arise from a di-π-methane like rearrangement of the borate.[6] As further support, they showed that the irradiation of (p-biphenylyl)triphenylborate gives 2,5,7,7-tetraphenyl-7-boratebicyclo[4.1.0]-hepta-2,4-diene (**2**) as the major photoproduct.[7]



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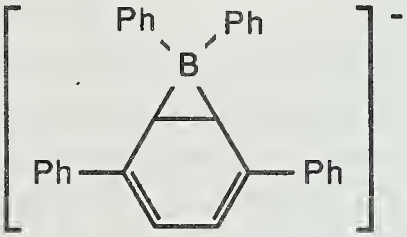

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Our interest has been in studying the photorearrangements of alkyltriphenylborates. We have investigated borates in which the alkyl group is unsaturated, to determine if the di-π-methane like rearrangements are indeed general for borates. Accordingly, the photolysis of triphenyl(styryl)borate (3)[8] and triphenyl(phenylethynyl)- borate (5), as their potassium or tetramethylammonium salts, have been studied. The irradiation of the all carbon analogs for both these borates have been studied, and give the tetraphenyl cyclopropane and cyclopropene products via the di-π-methane pathway.[9] The borate analogs, the boratirane **4** and boratirene **6**, the first reported examples of tetraaryl boron in a three-membered ring, have been isolated from the photolysis of borates **3** and **5** respectively.

The trans-1,1,2,3-tetraphenylboratirane (5) is a thermally stable, air and moisture sensitive,

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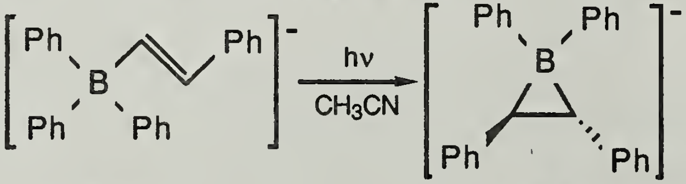
colorless solid. The structure was determined by spectroscopic data, and confirmed by x-ray crystallography. This compound has a remarkably low oxidation potential. Its reactivity has been studied, and with oxygen gives stilbene oxide and a borateolane derivative.

The 1,1,2,3-tetraphenylborateirene (**6**) is an extremely air and water sensitive yellow solid. The structure is assigned by spectroscopic data and confirmed by x-ray crystallography. Its reactivity is currently being studied.

Overall, it appears that this rearrangement is general for these borates, and this chemistry provides a route to a variety of unique strained borate species.



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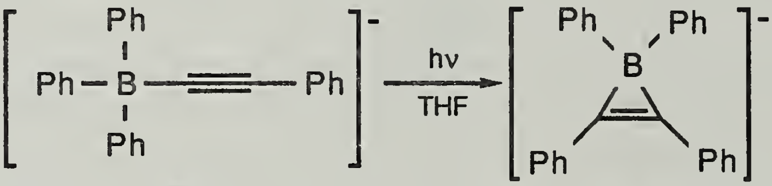

5 **6**

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ORGANOLEAD COMPOUNDS AND THEIR SYNTHETIC APPLICATIONS

Reported by David E. Reichert October 3, 1988

INTRODUCTION

Although the development of organometallic reagents capable of carbon - carbon bond formation has been important in organic synthesis, until recently the chemistry of organolead compounds has largely been unexplored. In this abstract the types and reactions of those organolead compounds which have been investigated for synthetic uses will be examined.

Prior to the development of the aryllead triacetates as reagents for the transfer of aryl, trifluoroaceto, vinyl, and ethynyl groups to a variety of substrates, very little use was made of organolead compounds. The first organolead compounds to be investigated were the ß - hydroxyalkyltriphenylleads which were found to undergo deoxymetallation to generate olefins. Halomethylplumbanes were investigated by Seyferth and coworkers as a source of dihalocarbenes. Recently it has been found that an allyllead species generated in situ can directly add to aldehydes, ketones, and imines. Tetraalkyl leads have also been found useful for the coupling of alkyl groups to acid chlorides, as well as for the addition of alkyl groups to aldehydes.

ß - HYDROXYALKYLTRIPHENYLPLUMBANES

The first organolead compounds to be studied for synthetic use were the ß - hydroxyalkyltriphenylleads. These compounds, generated from the nucleophilic ring opening of epoxides by an alkali - organolead compound were found to undergo deoxymetallation to generate olefins[1] . Considering the wide variety of reagents which also cause this transformation, many under much milder conditions and in higher yields, this reaction would seem to be of little use in organic synthesis.

HALOMETHYL PLUMBANES

Dihalocarbenes have proven valuable as intermediates in synthetic chemistry. Several methods for generating dihalocarbenes exist and are used in synthesis. The three major methods are: the treatment of organic trihalomethyl anions with strong bases such as potassium t - butoxide; the decarboxylation of alkali metal salts of trihaloacetic acids; and thermolysis of phenyl(trihalomethyl)mercury compounds[2]. This last method developed by Seyferth perhaps provides the best method due to its generally high yields of reaction product and mild reaction conditions[3]. Seyferth and coworkers studied the use of organolead compounds as a source of halocarbenes, and found that they, just like halomethyl mercurials, do generate halocarbenes upon thermolysis[3]. In this study Seyferth found that Ph_3PbCCl_3, Ph_3PbCBr_3, $Ph_3PbCHCl_2$,

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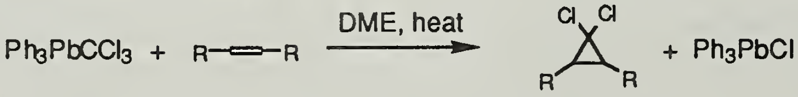
Ph_3PbCCl_2PH, upon heating gave dihalocarbene which then reacts with an olefin to generate the dihalocyclopropane in quite high yields (87 - 100 %). This reaction is shown in equation 1.



(1)

In comparison of the halomethyl lead compounds and halomethyl mercury compounds he found that the plumbanes reacted much slower. In order to increase the reaction rate to obtain a useful yield of product the reaction temperature had to be raised significantly, from 85° to 125° C. At the elevated temperatures product decomposition is a possibility which could limit the usefulness of the organolead method.

Seyferth feels that the reason for the lower reactivity of the lead compounds relative to that of the mercurials is two fold; first the Pb - C bond is 4 kcal/mol stronger that the Hg - C, and secondly the three phenyl groups provide more steric hindrance towards the intramolecular nucleophilic halogen attack which forms the dihalocarbene than does the lone phenyl group on the mercurial. It would thus appear that halomethylplumbanes are not particularly useful for the generation of dihalocarbenes although it may sometimes prove easier to generate the lead compound than it would be to generate a particularly unstable mercurial.

ARYLLEAD TRIACETATES

The first type of organolead compounds to have a definite synthetic utility were the aryllead triacetates. Pinhey and his coworkers found that these compounds provide a versatile method of transferring an aryl group including heteroaryls[4] to electron rich aromatics[5] and phenols[6] to generate biaryls and arylcyclohexadienones respectively. Further study found that aryllead triacetates will also substitute the aryl group for the acidic hydrogens of ß - diketones[7], ß - ketoesters[8], enamines[9], α - hydroxymethylene ketones[10], derivatives of malonic acid[11], and nitroalkanes[12].

Preparation Of Aryllead Triacetates

One method by which aryllead triacetates can be prepared is through direct plumbylation of the desired aromatic compound with lead tetraacetate or a lead tetrahaloacetate under acidic conditions. De Vos has shown that a wide variety of aryllead triacetates can be prepared in moderate to high yields by this method[13a - c]. The reaction is generally thought to proceed through a S_E2 mechanism, which explains the increase in rate as the aromatic substrate becomes more electron rich, and why aromatic compounds less electron rich than p - fluorobenzene fail to react. Stock and Wright have investigated this reaction and conclude that it is a typical electrophilic substitution reaction[14]. The aryllead triacetate is not obtained directly in this reaction, upon workup with water an oligomeric plumboxane of the general formula $[(ArPbX_2)_2O]_n$ is formed. When this is treated with excess acetic acid the desired aryllead triacetate is obtained. This method however has several limitations. The first is that the arene must be able to tolerate the required haloacetic acids. Another limitation is that only the para - substituted compound is formed in the case monosubstituted arenes. If any other isomer is desired it is necessary to use a different method of preparation.

A second method by which these compounds can be synthesized involves a procedure developed by Criegee[15]. This reaction involves a transmetallation between a diaryl mercurial and lead tetraacetate as shown in equation 2.

$$Ar_2Hg + Pb(OAc)_4 \longrightarrow ArPb(OAc)_3 + ArHgOAc \qquad (2)$$

This method however has several drawbacks. The first is that it is difficult to separate the aryllead triacetate and the arylmercury acetate. A second problem is that only one of the aryl groups from the mercurial is transferred which is a drawback if the aryl group is in limited supply. However Pinhey and Kozyrod found that the aryllead triacetate could be produced in situ eliminating the need for isolation with only a small decrease in the overall yield[16]. All attempts to prevent the wastage of one equivalent of aryl group from the mercurial proved fruitless.

The method of choice for the preparation of aryllead triacetates was found to be a transmetallation involving a Sn - Pb exchange[17]. In this reaction between an aryl tributyltin and lead tetraacetate, shown in equation 3, a mercury (II) compound typically $Hg(O_2CCF_3)_2$, when used as a catalyst leads to a much higher reaction rate.

$$ArSnBu_3 + Pb(OAc)_4 \xrightarrow{Hg(II)} ArPb(OAc)_3 + Bu_3SnOAc \qquad (3)$$

A variety of arylstannanes with aryl groups ranging from benzene to p - trifluoromethylbenzene have been found to work in this reaction. This method avoids the difficulties inherent in the Pb - Hg exchange as only one equivalent of the aryl group is needed, and the tributyltin acetate produced is easily removed from the reaction.

Reactions Of Aryllead Tricarboxylates

Synthesis of biaryls. Aryllead tricarboxylates are useful as a method to synthesize a wide variety of biaryls usually in quite good yields[5,6,18a - b]. Prior to the development of this method, biaryls were prepared via the Ullman reaction[19a], the Gomberg - Bachman reaction or a derivative[19b], or by substitution of an arene with an aryl radical. The aryl radical could be produced by the decomposition of aryl peroxides or by the photolysis of aryl iodides[19c] or arylthallium bistrifluoroacetates[19d]. All of these methods are limited either by the required reaction conditions or the generally low yields obtained.

Aryllead tricarboxylates provide a more general and higher yielding method for the synthesis of both symmetrical and unsymmetrical biaryls. Depending on the type of aromatic substrate with which the aryllead triacetate is reacted different reaction conditions or catalysts are required. For example most arenes will react when trifluoroacetic acid is used as the solvent; moderately electron rich arenes such as toluene will react in neutral solvents with $AlCl_3$ as a catalyst. Electron rich arenes such as alkyl substituted phenols react without need of a catalyst .

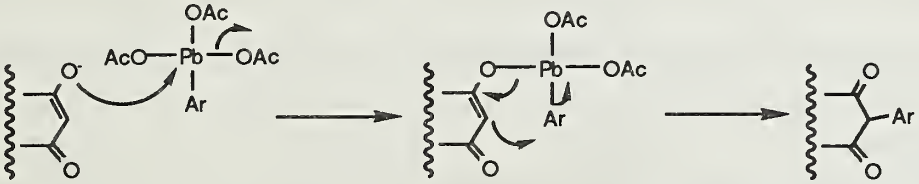
These reactions are believed by Pinhey to proceed through an electrophilic attack on the aromatic substrate, presumably by an aryl cation. Several observations were taken to support this, first the reaction rate increases as the electron density of the substrate increases and secondly, the isomer distribution in the biaryl products was found to compare well with reactions generally believed to involve aryl cations. A free radical mechanism is ruled out by Pinhey on the basis that no products arising from attack on any methyl group of a substrate has been observed. Additional support for the reaction not occurring by a radical mechanism comes from the work of Barton who studied the reaction of phenyllead triacetate with a ß - ketoester both in the presence and absence of a spin trap and found no difference in the yield of arylated product[20a].

Pinhey however feels that free aryl cations cannot be reaction intermediates under the reaction conditions used[5]. He assumes that if the rate determining step is the cleavage of the Pb - C bond, which produces the aryl cation, then aryltrifluoroacetates should be produced. Yet biaryls are produced faster than the aryltrifluoroacetates. In a study of the reaction rates of p - $FC_6H_4Pb(OAc)_3$ with various methylated benzenes, he found that the reaction rate increased as the ability to stabilize a π complex did. He therefore proposes the formation of a π complex between the aryllead triacetate and the aromatic substrate, followed by the rate determining cleavage of the Pb - C bond. This formation of a π complex would explain why the formation of the biaryl proceeds faster than trifluoroacetylation. The π complex then rearranges to give the final product.

Arylation of enols. Aryllead triacetates have also found use in the synthesis of α-arylated carbonyl compounds[7 - 11]. Unlike the synthesis of biaryls very few methods of aryllating enols exist. The only known methods are the treatment of the enol with diphenyliodonium salts[21a], or the copper catalyzed arylation of ß - diketones with 2 - bromobenzoic acids[21b]. A more recent development are the pentavalent organobismuth reagents developed by Barton[20a - d]. Aryllead triacetates have been found to react with ß - diketones, ß - ketoesters, malonic ester and barbituric acid derivatives, silyl enol ethers, enamines, and α - hydroxymethylene ketones. These reactions are particularly useful due to the generally mild conditions required for arylation. A typical reaction involves dissolving the substrate and a slight excess of aryllead triacetate in chloroform with one equivalent of pyridine and warming to 40° C.

Pinhey proposes that the reaction could occur through two possible mechanisms, a nucleophilic displacement or a radical process involving electron transfer from the enolate anion to the aryllead triacetate[7]. The nucleophilic displacement shown in Scheme I is felt to be more likely. The free radical mechanism would again be disfavored in light of the study by Barton[20a].

Scheme I



Arylation of nitroalkanes. Nitroalkanes which have acidic protons can also react with aryllead triacetates, however in these reactions it was found that DMSO provided higher yields than the previously used $CHCl_3$ / pyridine[12]. As was found with malonic esters the sodium salts of the nitroalkanes will react to give the aryllated product, usually much faster than the unionized nitroalkane.

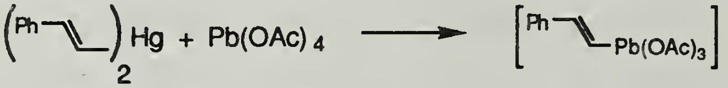
Limitations of aryllead tricarboxylates. These reactions do have several limitations, the first being sensitivity to steric effects. If the position to be arylated has a sterically bulky substituent such as a t- butyl group near it, the reaction either gives a poor yield or fails. Another disadvantage is that cyclic substrates with two α hydrogens will only produce the diarylated products. It proved impossible to obtain the monoarylated product despite all efforts. These reactions also suffer from a lack of stereocontrol and an extremely long reaction time, up to 48 hrs in some cases. The long reaction time, is a primary disadvantage relative to the alternative arylation method developed by Barton[20a-d]. He has shown that the pentavalent organobismuth reagents; Ph_4BiOTs, $Ph_4BiOTFA$, Ph_3BiCl_2 undergo the same types of reactions as shown for aryllead triacetates, usually much faster. The aryllead triacetates however are not as wasteful of the aryl group which could be of major importance if it is in limited supply. A recent review has appeared which compares and contrasts the recent methods of arylation.[22]

Aryllead triacetates have found use in synthetic applications. Their ability to transfer an aryl group to enolizable carbonyl compounds have been used for the synthesis of 5,5,10b - trimethyl - cis 4b,5,6,10b,11,12 - hexahydrochrysene - 2,8 - diol[23]; the drugs ibuprofen and phenobarbital[24] ; and the alkaloids (±) - o - methyljoubertiamine, (±) - mesembrine, and (±) - lycoramine[25 a,b] .

ALKENYL AND ALKYNYL LEAD TRIACETATES

An important reaction in organic synthesis is the introduction of a vinyl group at the α position of a carbonyl group. The usual method is by the introduction of some group which in subsequent steps produces the double bond. There are other methods however, which directly introduce the alkenyl group. One involves the nickel catalyzed coupling of a vinyl halide to lithium ester enolates[26]. The second method involves the coupling of a Reformatsky reagent and a vinyl halide in the presence of $Ni(PPh_3)_4$ or $Pd(PPh_3)_4$[27]. Both methods provide moderate yields of the alkenylated products, however both are limited as to the types of substrate which can be successfully used.

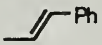
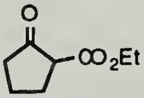
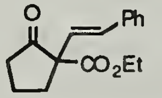
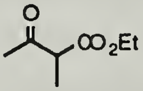
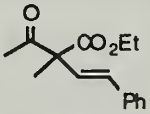
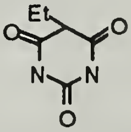
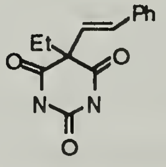
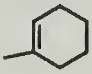
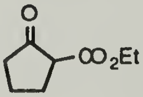
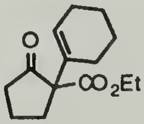
Recently Pinhey and coworkers have presented evidence that lead triacetates can transfer vinyl groups. It would appear that these compounds provide a method for the direct introduction of alkenyl groups to ß - ketoesters[28]. As with the aryl reagents the organolead species can be generated by reaction of $Pb(OAc)_4$ with the vinyl stannane as shown in equation 4 .



(4)

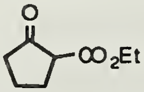
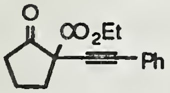
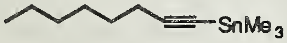
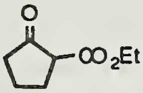
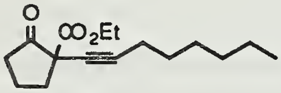
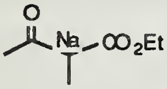
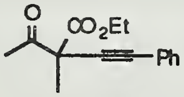
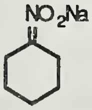
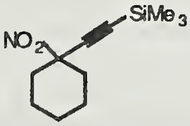
This method could prove useful as a variety of enols have been shown to be capable of reacting with the alkenyllead compounds, some examples showing the utility of this reaction are found in Table I.

Table I Reactions of Vinyllead Triacetates with Various Enols

$RPb(OAc)_3$	Substrate	Product	Yield
R = 			65 %
			52 %
			66 %
			80 %

In a preliminary communication Pinhey reports that the addition of a ß - ketoester to the mixture produced by the reaction of $Pb(OAc)_4$ with various ethynyltrimethylstannanes will produce the α - alkynylated product in good yield[29]. Some examples of this reaction showing a variety of alkynes and substrates found to be successful, are shown in Table II.

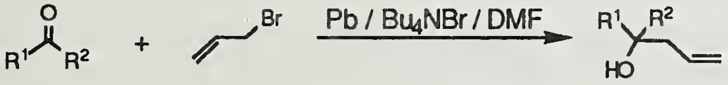
Table II Reactions of Alkynyllead Triacetates

Stannane	Substrate	Product	Yield
$Ph{-}{\equiv}{-}SnMe_3$			78 %
			77 %
$Ph{-}{\equiv}{-}SnMe_3$			58 %
$Me_3Si{-}{\equiv}{-}SnMe_3$			60 %

The only other procedure for accomplishing this type of reaction involves the condensation of a chloroacetylene with a lithium enolate[30]. The alkynyllead triacetates therefore provide a method for the introduction of an alkynyl group to compounds which are unstable to LDA or similar bases.

LEAD PROMOTED ALLYLATION

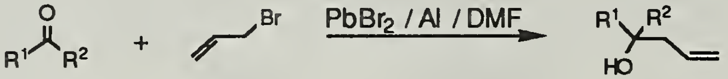
In 1986 it was reported[31] that allyl groups could be efficiently transferred to carbonyl compounds by treatment with allyl bromide and Pb (0) as shown in equation 5.



(5)

This reaction showed great chemoselectivity with a reactivity order: RCHO > R^1R^2CO > $R^1CH(OH)CO_2R^2$ > > $R^1CO_2R^2$, lactone, acid anhydride, and RCOCl. The authors suggest that the reaction occurs through a Pb (II) species based on the stoichiometry of the reaction. It was also found that the yield of product dropped precipitously when Bu_4NBr was absent, and that other amine salts had no effect.

One year later it was found that this reaction could be accomplished by using a catalytic amount of $PbBr_2$ with Al foil used to generate the Pb (0) required for the formation of the active species[32a]. This reaction is shown in equation 6.



(6)

Again very little information is presented regarding the mechanism, however some divalent lead species appears to be involved as no reaction occurs in the absence of $PbBr_2$. The authors do report that the reaction is catalytic with a turnover of 14 - 77. These reaction conditions were also found to allylate a variety of imines as well as carbonyl compounds[32b].

A large number of metals and their organic derivatives have been shown to be capable of adding an allyl group to a carbonyl functionality, some of these include Sn, Zn, Mn, Bi, SmI_2, and Ce[33]. Lead provides yet another method of accomplishing this reaction, yet one with some important advantages. First the reaction displays a very high chemoselectivity which is important for substrates possessing more than one carbonyl functionality. A second benefit is the low cost and commercial availability of the reagent.

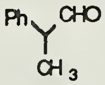
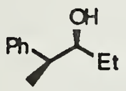
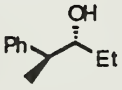
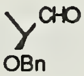
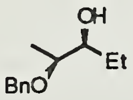
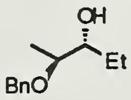
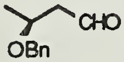
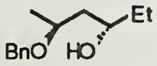
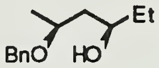
TETRAALKYLLEADS

Numerous methods for the addition of alkyl groups to carbonyl functionalities exist. Grignard reagents, organolithiums and cuprates are most common. With few exceptions these classical reagents must be prepared before use and are air and moisture sensitive. Tetraalkyl lead compounds are readily storable in air and have no moisture sensitivity. Recently tetraalkylleads have been found by Yamada and Yamamoto to be able to transfer an alkyl group to acid chlorides when catalyzed by Pd (0)[34]. Unlike the similar reaction of tetraalkyl stannanes, these reactions occur quite rapidly under milder conditions. This reaction is illustrated in equation 7.

$$R'COCl + R''_4Pb \longrightarrow R'COR'' + R''_3PbCl \qquad (7)$$

The same authors report that tetraalkyl lead compounds react selectively with aldehydes with high 1,2 and 1,3 asymmetric induction in the presence of $TiCl_4$ or BF_3[35]. Under the same conditions ketones are entirely non - reactive. Yields for this reaction range from 32 % for $(C_6H_{11})_4Pb$ with $C_6H_{11}CHO$ to 98 % for $(Et)_4Pb$ with $C_6H_{11}CHO$. The enantiomeric ratios obtained with the tetraalkyl lead compounds are significantly better than those obtained with Grignard and alkyl zinc reagents. Table III shows the asymmetric induction obtained in this study.

Table III Alkylation of Aldehydes

Aldehyde	Tetraalkyllead	Products	
	Et_4Pb	 93	 7
	Et_4Pb	 98	 2
	Et_4Pb	 78	 22

SUMMARY

Although organolead compounds have not been extensively used in organic synthesis, they are reagents with the potential for wider use. At present the aryllead tricarboxylates have been the most studied and have been developed into a useful method of introducing aryl groups α to enols. Aryllead tricarboxylates also provide a direct and efficient method for the preparation of biaryls, both symmetrical and unsymmetrical. Alkenyl and alkynyl lead triacetates could prove versatile for the introduction of vinylic and acetylenic groups α to carbonyl groups. These reagents however require more study in order to determine the generality and scope of their reactions. At present only a few examples of each have been shown. The recent discoveries of the lead promoted allylation of carbonyls shows promise, especially with preparative scale reactions in which the catalytic lead system could provide major savings in cost. Tetraalkyllead compounds have been shown to show promise as reagents for the transfer of alkyl groups to acid chlorides and aldehydes.

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EFFICIENT, MULTICOMPONENT RING FORMING REACTIONS

Reported by Keith W. Woods October 31, 1988

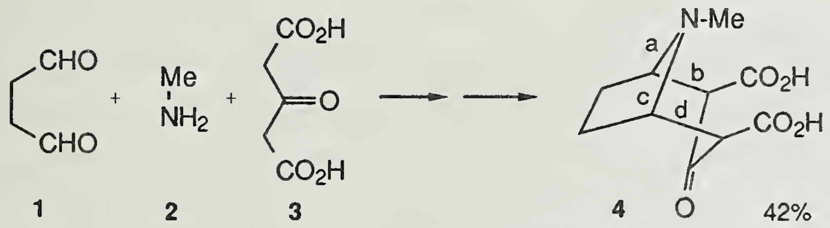
INTRODUCTION

The formation of carbon-carbon bonds is of fundamental importance to synthetic organic chemistry. The selective formation of multiple carbon-carbon bonds by reactions of multiple components in a single reaction vessel can be especially efficient. A variety of well known organic reactions including the Diels-Alder and dipolar cycloadditions, the Robinson annulation, and the α,β-dialkylation of α,β-unsaturated carbonyl compounds achieve this goal for the formation of two new carbon-carbon bonds. Chemoselective multicomponent, one-pot syntheses in which three or more bonds are formed in an efficient manner is a greater challenge due to the multiplicity of reaction pathways available to multiple functionalities present. This concept has attracted attention in recent years and has led to a number of successful conversions of simpler molecules specifically and efficiently into more complex molecules.[1] In this abstract a number of different methods which have been developed for the construction of three or more bonds in a single operation will be discussed with emphasis on three- and four-component systems.

NITROGEN HETEROCYCLES

Synthesis of nitrogen heterocycles provides a number of examples which illustrate the advantages afforded by multicomponent, one-pot cyclizations. The procedures to be considered here are of two general types. The first type is based on the Mannich reaction and the second is based on conjugate addition.

Probably the most famous one-pot cyclization is the classic Robinson-Schöpf synthesis of tropinone 4 (eq. 1).[2] Condensation of succindialdehyde 1 with acetonedicarboxylic acid 3 and methyl amine 2 under physiological pH conditions followed by decarboxylation yields tropinone 4 in 42% yield. Glutardialdehyde yields the analogous 9-membered bicyclic product in 58-68% yield.[3] This double Mannich condensation efficiently forms four new bonds from three different components in a single operation.



(1)

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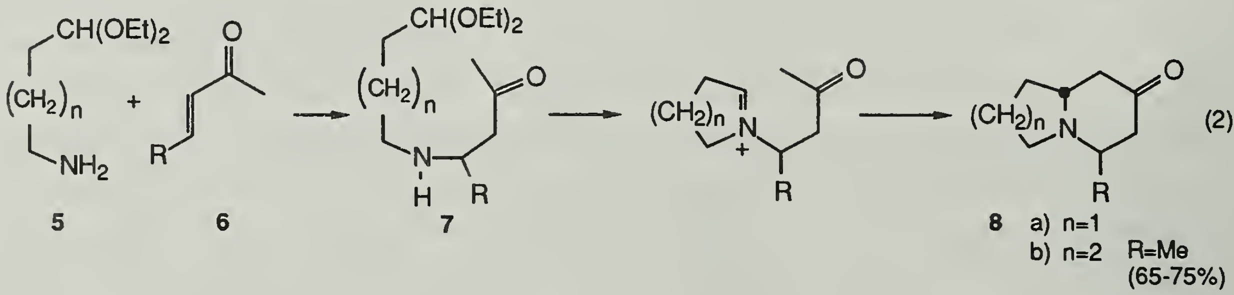
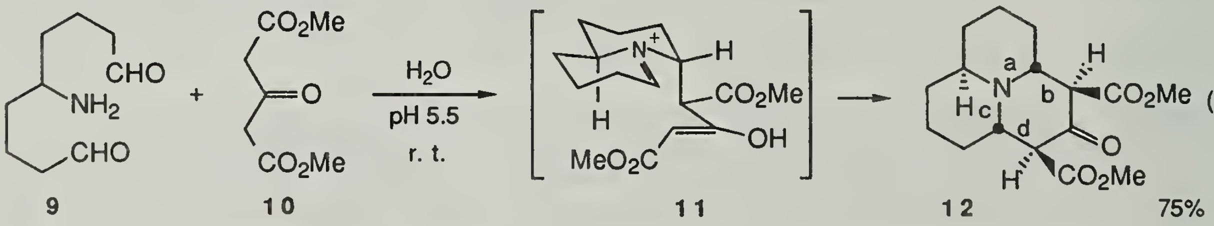
In his work on the synthesis of quinolizidines and indolizidines King found that a modification of the Robinson-Schöpf tropinone synthesis could be applied to the synthesis of indolizidines and quinolizidines to achieve substitution in either ring[4]. Treatment of 4-aminobutanal diethyl acetal with dimethyl acetonedicarboxylate and acetaldehyde yielded **8b**, after hydrolysis and decarboxylation, as a 3 : 1 mixture of stereoisomers in 75% yield. Simplification to a two-component system still allowed formation of three new bonds in a single vessel with similar yields but with greater flexibility (eq. 2). In the latter case, addition of diethyl



(2)

acetals of α-amino-ω-aldehydes **5** to α,β-unsaturated ketones **6** produced amino ketone intermediates **7** which when extracted into 2M HCl induced hydrolysis of the acetal and cyclization to the respective quinolizidines and indolizidines **8**. Of the standard methods attempted, neither Dieckman cyclization of a diester nor reduction of an imide and subsequent formic acid cyclization gave acceptable yields of the desired compounds.

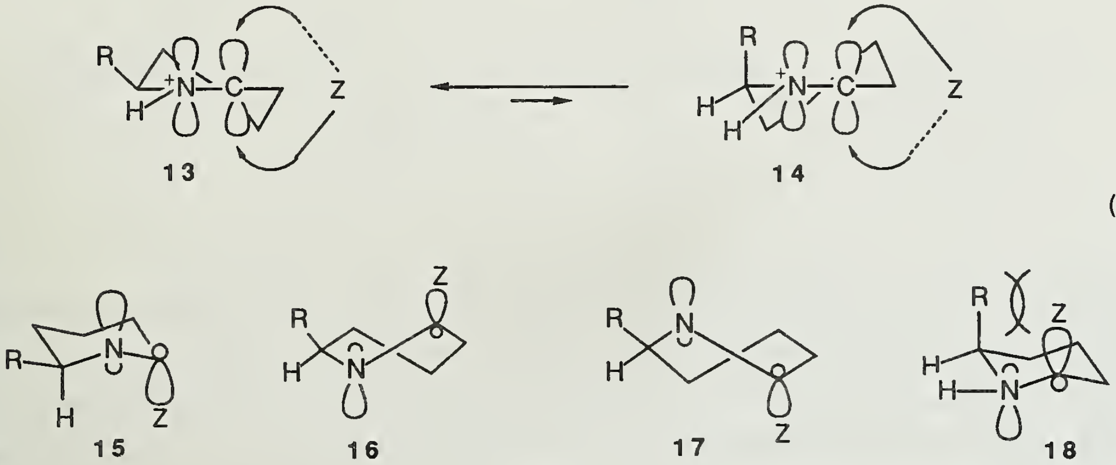
Stevens' total synthesis of ladybug (*Coccinellidae*) defense alkaloids similarly involves a double Mannich condensation[5]. The key step combines amino dialdehyde **9** and methyl acetonedicarboxylate **10** via an intermolecular followed by an intramolecular Mannich condensation (eq. 3). This transformation results in the formation of four new bonds (a-d),



(3)

five new chiral centers, and three new rings in 75% yield (ca. 93% yield per bond formed) from achiral starting materials. This substantial increase in structural and stereochemical complexity very nicely illustrates the great synthetic advantage of such one-pot cyclizations.

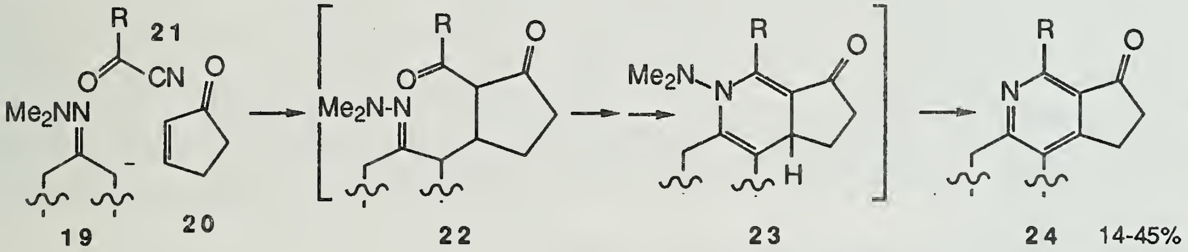
The stereochemistry in **12** is a result of kinetic control. Although the side chain would prefer to be equatorial, axial orientation in **11** positions the reaction centers in proper alignment for ring closure. This arrangement of the nucleophilic and electrophilic centers is set in the initial Mannich reaction of conformers represented as **13** and **14**. Of the possible transition states where proper orbital overlap is maintained, **16** and **17** require boat-like transition states and **18** has an unfavorable 1,3-diaxial interaction between the side chain and the incoming nucleophile (eq. 4).



(4)

The remaining transition state **15** does not have these unfavorable interactions and is the preferred transition structure which leads to the observed stereochemistry.

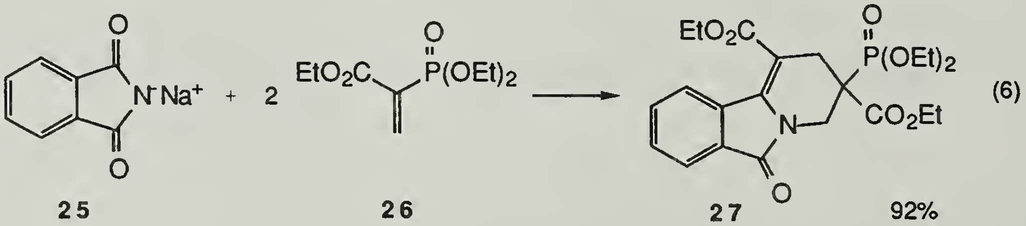
Kelly and Liu have developed a general pyridine synthesis utilizing a one-pot operation initiated by a conjugate addition reaction (eq. 5).[6] Cyclization of *N,N*-dimethylhydrazone anions



(5)

19, α,β-unsaturated ketones **20**, and acyl cyanides **21** by a Michael addition followed by a Claisen condensation and then 1,6-carbonyl addition forms the ring. Elimination of water and dimethyl amine leads to generation of the aromatic system in 14-45% overall yield. The yield limiting step may be the ring closure. This may be partly due to tautomerization of the diketone intermediate **22**. Even though the yields of pyridines are only moderate by this method, the simplicity with which complex pyridine systems can be directly constructed from simple starting materials offsets the yield deficiency. This method avoids side reactions encountered in the classical Knoevenagel route to pyridine synthesis and provides a means of assembling a pyridine nucleus having up to five different substituents in a one-pot operation with full regiochemical control.

Another one-pot sequence initiated by conjugate addition leading to nitrogen heterocycles is that discovered by Minami and co-workers (eq. 6).[7] Treatment of phthalimide anion **25** with two



25 **26** **27**

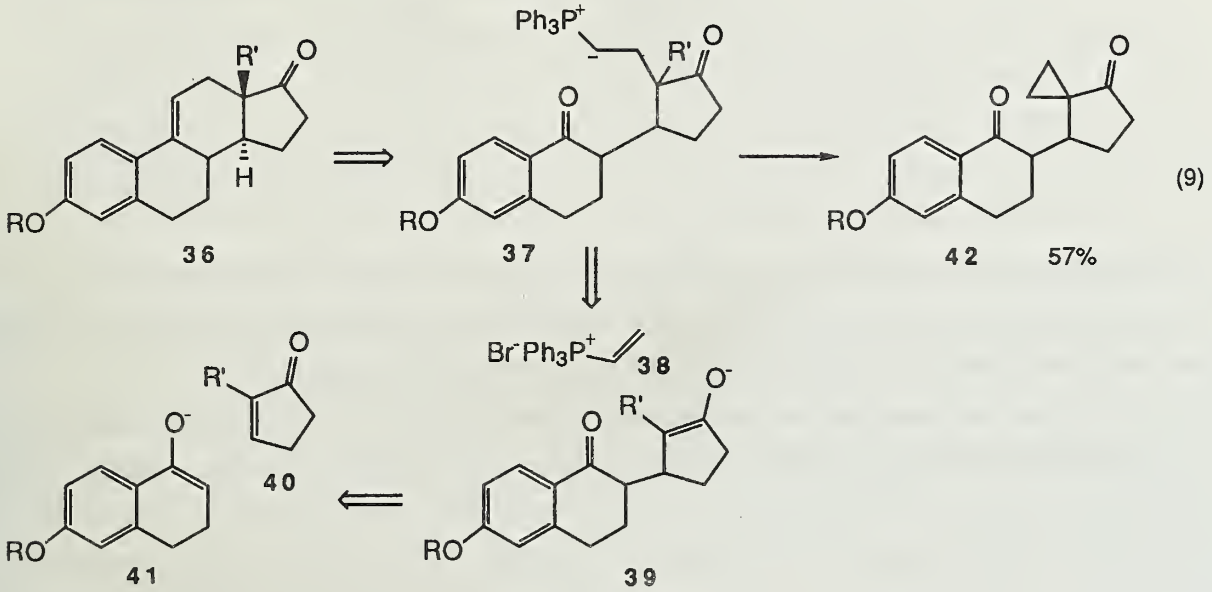
molar equivalents of vinylphosphonate **26** yields **27** in 92% yield as a result of two Michael additions followed by an intramolecular Wittig-Horner reaction. Similar treatment of the vinylphosphonate with the anions of maleimide, succinimide, and glutarimide produces the corresponding indolizine and quinolizine derivatives in 19-57% yield. The examples described above demonstrate the ease with which complex nitrogen heterocycles can be efficiently assembled from multiple components in one-pot processes.

CARBOCYCLES

Carbocycles have also been rapidly and efficiently assembled by multicomponent, one-pot techniques. Many of the processes are initiated by Michael additions. The main emphasis here will focus on the sequence of reactions involving two Michael reactions followed by ring closure. This process has been termed MIMIRC (Michael-Michael ring closure) by Posner[8]. The discussion will begin with examples of limited application and progress toward procedures of greater generality. Four-component systems will be presented separately from two- and three-component systems.

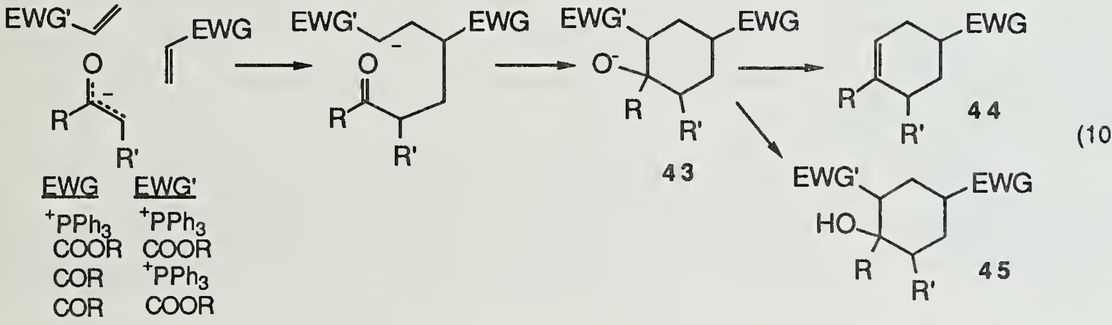
Two- and Three-Component Systems

Cory and co-workers have reported a series of methods for the bicycloannulation of cyclohexenes and cyclohexenones to give the tricyclo[3.2.1.0]octane ring system in a one-pot operation.[9] Their cyclohexenone bicycloannulation is considered to involve three mechanistic steps (eq. 7). The kinetic (α') enolate of the enone **28** undergoes an initial conjugate addition to an activated olefin. The activating group Z exhibits dual character functioning first as an electron withdrawing group and later as a leaving group. The stabilized anion which results **29** reacts through an intramolecular Michael addition to the enone moiety. This resulting enolate **30** then displaces the leaving group Z to form the cyclopropane ring of the tricyclooctanone **31**. Vinyl reagents in the form of phosphonium salts, sulfones, and nitro olefins have all been used cyclopentenone **40** (R' = Me) as the first Michael acceptor and then treatment with vinyltriphenylphosphonium bromide **38** yielded steroid **36** (R = R' = Me) in 8.4% yield (21.3% based on consumed tetralone). This tandem MIMIRC reaction represents a one step 19-nor steroid total synthesis involving connection of a 10-carbon, a 6-carbon, and a 2-carbon unit in a single reaction vessel.

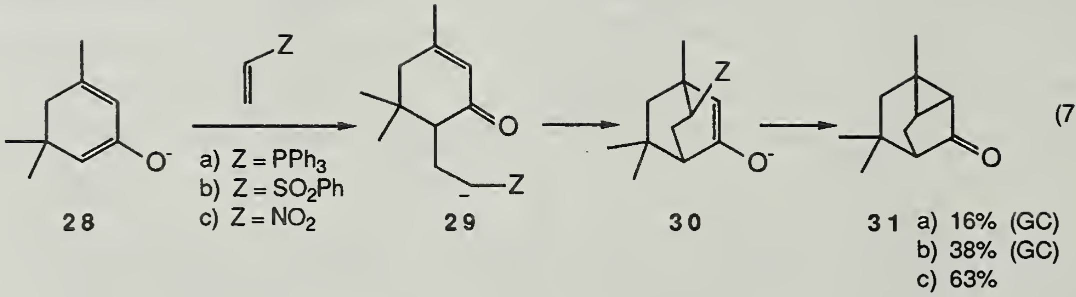


The Michael reaction between tetralone enolate **41** and 2-bromo-2-cyclopentenone **40** (R' = Br) followed by treatment of the resulting enolate **39** with **38** yielded the spirocyclopropyl ketone **42** in 57% yield. In this process the carbon α to the ketone carbonyl in **40** acts first as a nucleophilic center and then as an electrophilic center. Study of α-haloenolate ions generated in other ways revealed that the reaction with **38** and then with aqueous hydroxide formed cyclopropyl ketones in good yield (60-70%).

Further extension of the MIMIRC work led to the development of a method for efficiently connecting three separate 2-carbon units in a 2+2+2 construction of phosphorus substituted cyclohexenes in a single pot (eq. 10).[11] Ketone enolate ions underwent tandem Michael



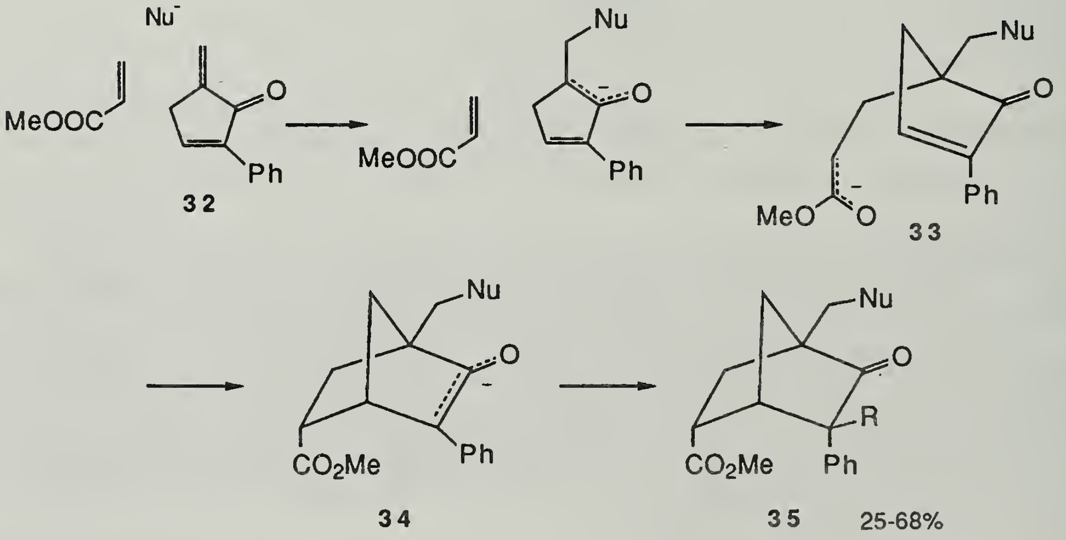
EWG	EWG'
$^{+}PPh_3$	$^{+}PPh_3$
COOR	COOR
COR	$^{+}PPh_3$
COR	COOR



(7)

successfully in this process to give **31** in 16% (GC), 38% (GC), and 63% respectively. This method makes the synthesis of tricyclooctanone available in a single step operation providing advantages of convenience and considerable savings of time and expense.

Another multicomponent cyclization procedure makes use of a three-component triple conjugate addition sequence (eq. 8).[10] This single operation procedure is considered to involve



(8)

regiospecific addition of a nucleophile to the exocyclic double bond of α-methylene cyclopentenone **32** followed by trapping of the resulting enolate with methyl acrylate. Finally, attack of that anion on the endocyclic double bond of the cyclopentenone results in the bicyclo[2.2.1]heptanone **35** after protonation (25-68% overall yield). An X-ray crystal structure has shown the ester and the phenyl groups of bicycloheptanone **35** (Nu = -SPh; R = H) to have an endo-endo relationship.

Retrosynthetic analysis of an estrone derivative of general structure **36** led Posner and co-workers to develop a MIMIRC sequence of reactions for the construction of steroids by formation of three carbon-carbon bonds in one reaction vessel (eq. 9).[8a] Use of 2-methyl-2-

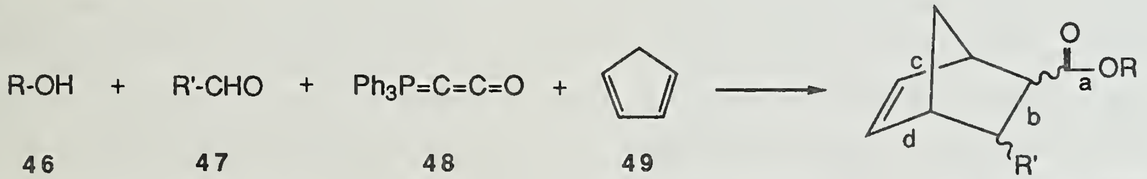
reactions followed by an intramolecular Wittig ring closure reaction. Hydrolysis of the cyclohexenyltriphenylphosphonium intermediate with hydroxide aids in ease of isolation of the product. Overall yields of the phosphine oxides ranged from 48 to 70%.

In addition to the MIMIRC reactions for one-pot 2+2+2 construction of phosphorus-substituted cyclohexenes, Posner and co-workers have found that alkoxycarbonyl-substituted cyclohexanols, acylcyclohexenes, and acylcyclohexanols can be prepared in similar fashion.[12] In all cases a ketone lithium enolate was added to two equivalents of a Michael acceptor and the culminating step was ring closure via either a Wittig olefination or an aldol reaction (eq. 10). In the early examples, two equivalents of the same Michael acceptor were used, but application of the MIMIRC sequence to the coupling of three different components has proven to be successful as well. Besides cyclohexanone enolates, 3-pentanone, and p-methoxyacetophenone were used successfully. These reactions have been run on gram scale in some cases. The multifunctionality of the cyclized products provides opportunity for many different types of further chemical manipulations. This triply convergent technique has been shown in a number of cases to represent a useful, easy, and convenient means of transforming relatively simple materials into structurally much more complex cyclic systems.

Four-Component Systems

The sequential, multicomponent reactions discussed to this point have involved the formation of polyfunctionalized and/or highly substituted ring systems from two or three components in a single reaction vessel. The ease and simplicity of this type of assembly has been demonstrated. Controlled coupling of four components in one reaction vessel is clearly an even more challenging endeavor offering even more useful products. A variety of examples from different laboratories serve to illustrate the attainment of this goal.

Bestmann and Schobert have provided two examples of a four-component one-pot cyclization.[13] Formation of four bonds follows a sequence of consecutive ketene addition, Wittig olefination, and Diels-Alder cycloaddition (eq. 11). An alcohol **46**, an aldehyde **47**, ketenylidenetriphenylphosphorane **48**, and a Diels-Alder diene **49** are all combined at the start of the reaction. The Diels-Alder adduct **50** is formed in 55-58% yield. The scope of this process was not investigated.



(11)

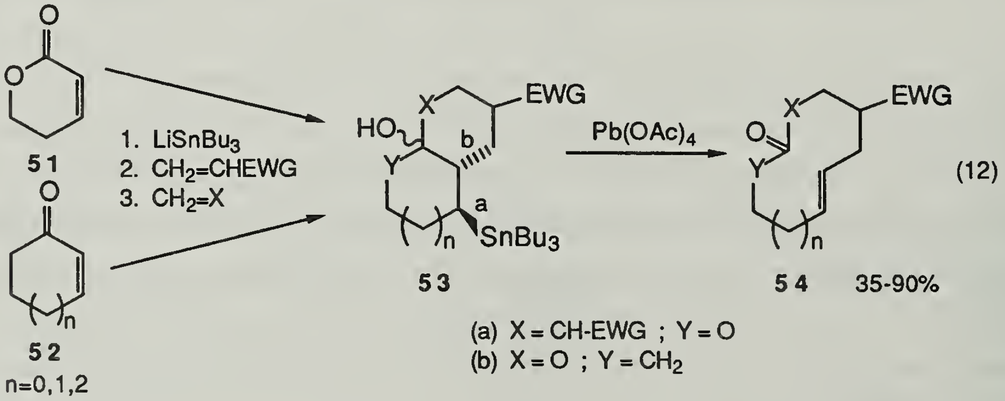
46 **47** **48** **49**

(a) $R = (nC_3H_7)_2CH$; R' = nPr
(b) R = (-)-Menthyl ; R' = Et

50 (a) 55% yield
(b) 58% yield

Another four-component example of unknown generality was reported by Thebtaranonth and co-workers (eq. 8).[10] They report the trapping of enolate **34** with electrophiles other than protons. The only specific example cited yielded the product **35** (Nu = -SPh; R = Me) in 61% total yield using methyl iodide as the electrophile.

Posner and co-workers have developed two easy one-pot procedures for forming four new bonds and constructing six-membered rings via a 2+2+2 connection (eq. 12).[14] The first procedure developed involves sequential Michael-Michael-Michael ring closure reactions and the latter process makes use of sequential Michael-Michael-aldol ring closure reactions. Both procedures are initiated by conjugate addition of tri-n-butyltinlithium to cyclic α,β-unsaturated carbonyl compounds. Oxidative fragmentation of the products by lead tetraacetate allows ring enlargement to unsaturated n+4 cyclic ketones and lactones. The double bonds formed are exclusively *trans* due to the *trans* relationship between bonds a and b in **53** and to the concerted *anti* elimination during the lead tetraacetate promoted oxidative fragmentation of the γ-hydroxystannane intermediate. Several of these transformations were carried out on gram scale. The products formed from this four-component cyclization-fragmentation sequence are of substantial synthetic potential.



CONCLUSION

The structural diversity of the examples cited herein, along with the ease, flexibility, and efficiency of their synthesis clearly demonstrate that the multicomponent, one-pot construction of polyfunctionalized ring systems is worthy of the research efforts invested thus far. This technique is of great appeal and value to preparative synthetic organic chemistry. Investigation into the design and execution of new multicomponent cyclizations forming multiple bonds in a single reaction vessel offers many opportunities for continued research.

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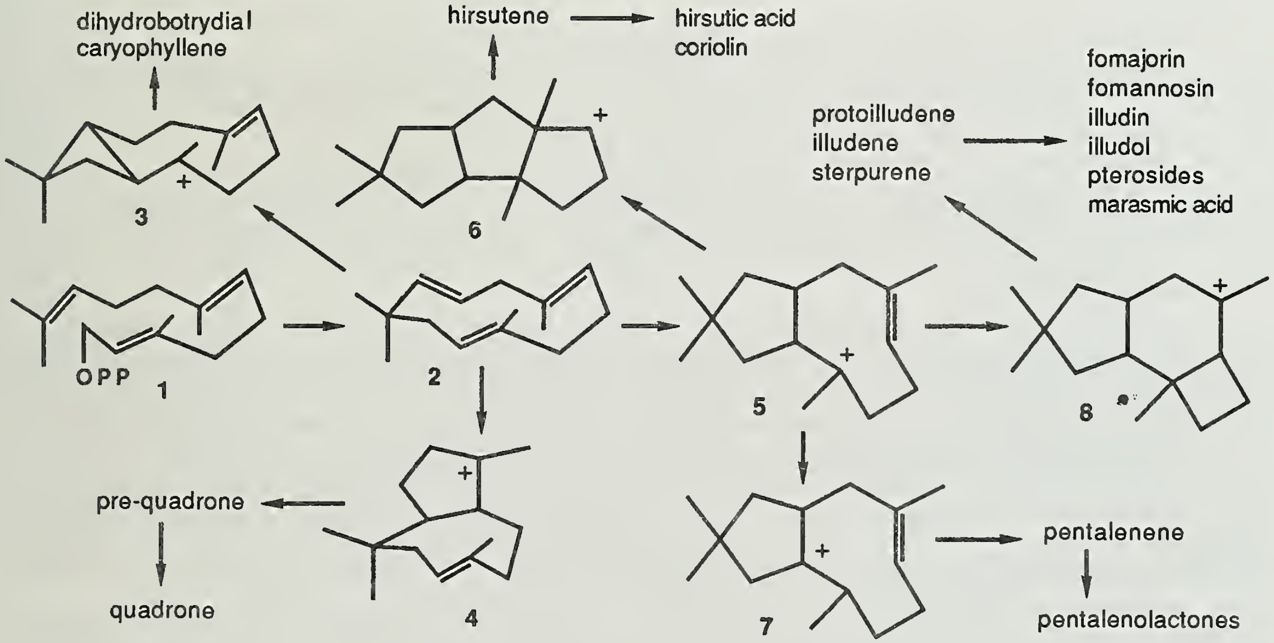
RECENT BIOSYNTHETIC STUDIES ON THE HUMULENE-DERIVED SESQUITERPENES: BIOSYNTHESIS OF QUADRONE AND PENTALENOLACTONES

Reported by Kwok N.Yee November 14, 1988

The humulene-derived sesquiterpenes have attracted considerable attention over the last two decades. These compounds have diverse structural features and exhibit a variety of biological activities, which include antibacterial, antitumor, and phytotoxic properties.[1] They are produced by fungi and the biosynthetic pathways to these metabolites have been intensively investigated by chemical and microbial degradations of isotope labelled incubation products.[2] The results are summarized in Scheme I. Biosynthetically, the generation of humulene (**2**) is proposed to proceed through ionization and cyclization of farnesyl pyrophosphate (**1**) by eletrophilic attack on C-11 and deprotonation at C-9.[3] Protonation of humulene (**2**), followed by further cyclizations and/or hydrogen or alkyl migrations of resulting carbocationic intermediates (**3** to **8**) leads to the formation of various natural sesquiterpenes. Included in this group are caryophyllene,[2,4] dihydrobotrydial,[2,5] hirsutic acid,[2] coriolin,[2] fomajorin,[6] fomannosin,[2] pterosides,[2] sterpurene,[7] illudol,[2] illudin,[2,8] marasmic acid,[2] quadrone,[9] and pentalenolactones.[3,10] Recent

Scheme I



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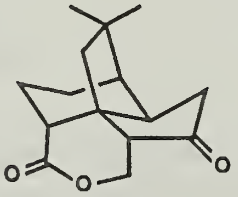
studies on the biosynthesis of quadrone (9) and pentalenolactones (**10**) have led to the formulations of new biosynthetic pathways for the humulene-derived sesquiterpenes.



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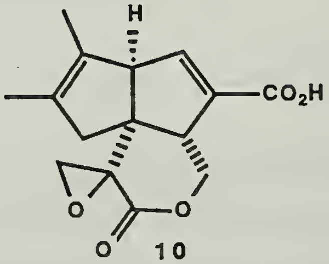

The relationship among humulune conformations, and their relationship to biomimetic transannular reactions and to biosyntheses of humulene-derived sesquiterpenes has been investigated by Shirahama and Matsumoto.[11]

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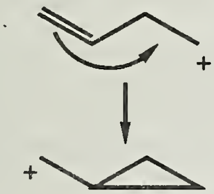
BIOSYNTHESES OF THE CYCLOPROPANE RING IN NATURAL PRODUCTS

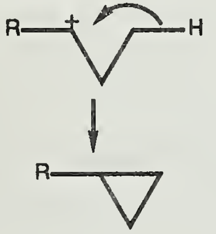
Reported by Hyung-Jung Pyun November 21, 1988

INTRODUCTION

Cyclopropane rings are frequently found in natural products. Although biosynthetic studies of these compounds have been done, there are still many compounds whose biosyntheses have not been examined. In this abstract, the biosynthetic pathways which place the cyclopropane ring in natural products and the biosynthetic studies which have been done to elucidate the cyclization mechanism and stereochemistry will be discussed. Generally, it has been proposed that the cyclopropane ring is formed by three types of reactions of carbocation intermediates. These are the homoallylic to cyclopropylcarbinyl cation rearrangement (eq 1) and 1,3-elimination (eq 2). In addition, there are some natural products in which the cyclopropane ring is formed by ring contraction from the cyclobutyl cations (eq 3).



(1)



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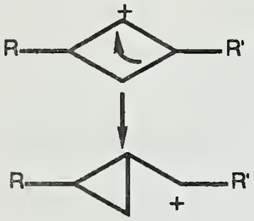

(3)

HOMOALLYLIC TO CYCLOPROPYLCARBINYL CATION REARRANGEMENTS

Cyclopropanation via homoallylic to cyclopropylcarbinyl cation rearrangement is considered to be the key step in the biosynthesis of the thujane family of monoterpenes. As an example, the biosynthesis of sabinene hydrate (**7**) is shown in Scheme I (**1**-**7**). Croteau and Hallahan elucidated the rearrangement of the homoallylic cation **5** to the cyclopropylcarbinyl cation **6** by converting the enzymatically derived **7a** and **7b**, which were derived from [1-^{3}H]GPP, to 2-keto-1,4-cineoles (**8**). The fact that base treatment of **8** removed the radioactivity confirmed that the label from [1-^{3}H]geranyl pyrophosphate (GPP, **1**) is located almost exclusively at the cyclopropylmethylene group (C-6) of **7**.[1] In addition, the rate difference of *exo*- and *endo*-proton exchange of **8** showed that the 1-*pro-R* hydrogen of the acyclic precursor gives rise predominently to the *exo*-α-hydrogen of **8**.[2] This result confirms that the configuration at C-1 of GPP is retained in the enzymatic conversion to (+)-*cis*- and (+)-*trans*-sabinene hydrate. Most of the thujane family monoterpenes, except α-thujene, are formed through oxidative metabolism of sabinene.[3, 4a]

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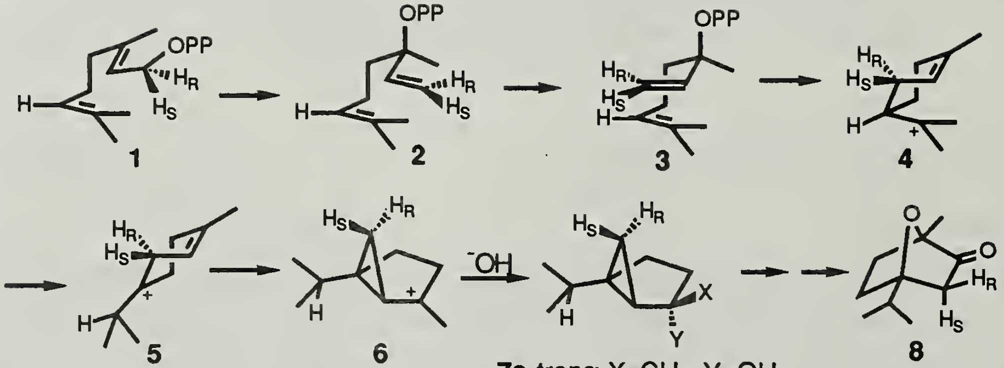
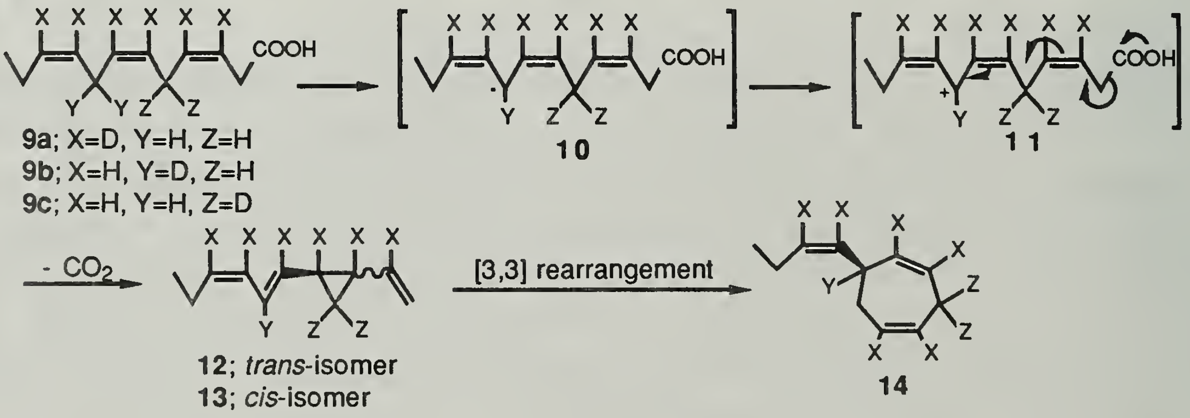
Scheme I



7a *trans*; X=CH_3, Y=OH
7b *cis*; X=OH, Y=CH_3

This type of cyclization is also found in the proposed biosynthetic scheme of (-)-hormosirene (**12**) and (+)-dictyopterene-A. These compounds which act as pheromones during the sexual reproduction of brown algae, are produced in minute amounts, so direct biosynthetic studies with female gametes of brown algae seemed unrealistic. Ectocarpene (**14**), however, one of the typical algal pheromones, is found in the essential oils of *Senecio isatideus*. In the biosynthesis of **14**, **9a**, **9b**, and **9c** were fed to *Senecio isatideus* and the product **14** was analyzed by GC-MS.[5] Although **12** was not isolated, the biosynthetic pathway to **14** via **13** has been proposed based on these results, as shown in Scheme II. Cyclopropanations via analogous rearrangements have been suggested for the biogenetic schemes of several sesquiterpenes including bicyclohumulenone, africanol, cubebene, and thujopsene.[6]

Scheme II



9a; X=D, Y=H, Z=H
9b; X=H, Y=D, Z=H
9c; X=H, Y=H, Z=D

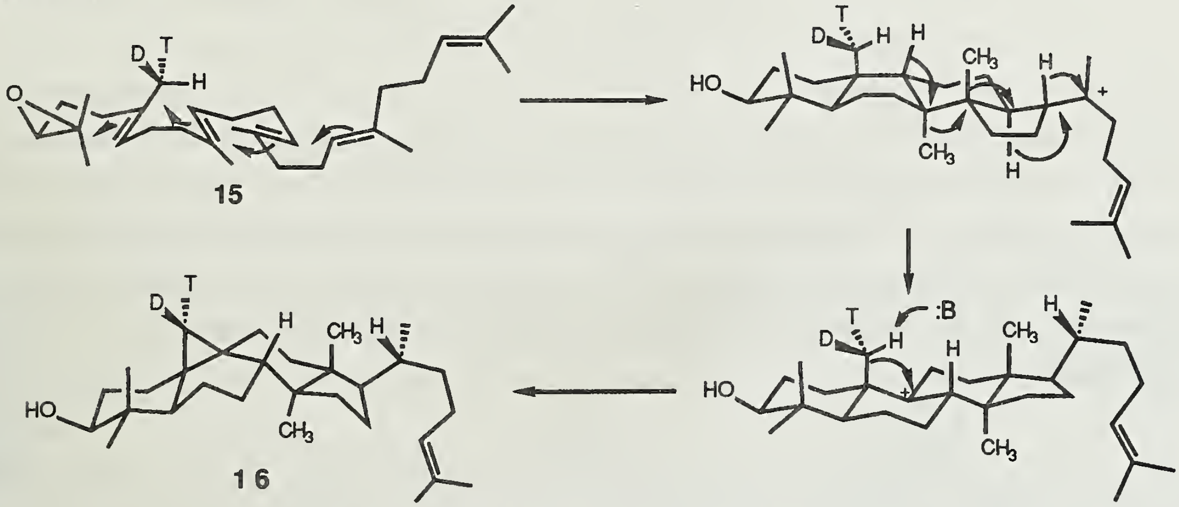
12; *trans*-isomer
13; *cis*-isomer

CYCLIZATION BY 1,3-ELIMINATION

1,3-Elimination of Carbocations and Alcohols

Cyclopropane ring formation via 1,3-elimination of carbocations is frequently suggested in terpene biosynthesis. Cycloartenol (**16**) is a very well known natural product in which the cyclopropane ring is believed to be produced by 1,3-elimination from a carbocation. A stereochemical study of this deprotonation with squalene-2,3-oxide bearing a chiral methyl group at C6, **15**, showed that the ring closure takes place with a methyl hydrogen replacement by C9 with retention of configuration if this methyl group is assumed not to migrate to C9 (Scheme III).[4d]

Scheme III



In contrast to sabinene and sabinene hydrate, α-thujene is apparently produced by a 1,3-elimination. In a biosynthetic study of γ-terpinene and α-thujene with a cell-free enzyme extract, the α-thujene enzymatically derived from [1-^{3}H]GPP was chemically oxidized to a keto-acid using $KMnO_4$.[7] Base treatment of the keto-acid resulted in the loss of radioactivity which means the cyclization occurs by deprotonation from C6, not by the double bond participation. It is surprising that among the thujane family of monoterpenes, only α-thujene is produced through this mechanism .

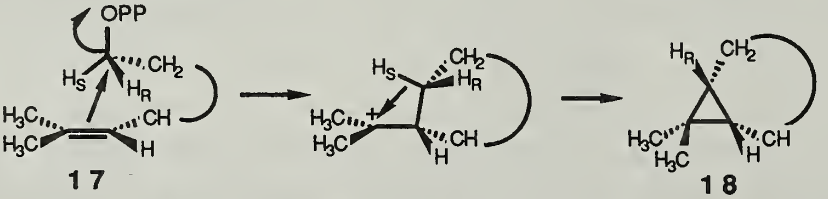
1,3-Elimination mechanisms have been proposed as key steps in many terpene biogeneses. For example, tricyclene type monoterpenes,[3] sesquiterpenes such as cyclosativene, cycloseychellene, longicyclene, and ishwarone,[6] as well as diterpenes such as devadorene, trachylobane, and helifulvane are all thought to be formed through 1,3-eliminations.[8]

There are some cyclopropane containing polyketide natural products. The cyclopropanation has been supposed to be 1,3-elimination instead of 1,2-elimination because a labeling study of cyclizidine biosynthesis showed that the cyclopropane moiety was apparently derived from propionate via 1,3-elimination.[9] Although the biosynthesis of indolizomycin[10] has not been studied, its structural similarity to cyclizidine makes it probable that it has a similar biosynthesis.

Cyclopropanation by Alkylation/1,3-Deprotonation on a Double Bond with Allylic Pyrophosphates as Electrophiles

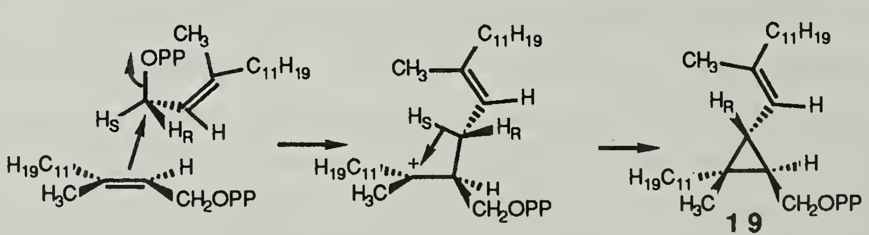
Casbene (**18**) is formed by the apparent insertion of a carbon electrophile into a double bond. In a study of its biosynthesis, incubations of geranylgeranyl pyrophosphates (GGPP, **17**) stereospecifically labeled at C1 provided the evidence that the *pro-S* hydrogen at C-1 is stereospecifically eliminated.[11] The stereochemical behavior of the C14-C15 double bond in casbene biosynthesis was elucidated by incubation of ^{13}C-labeled GGPP derived from [2-^{13}C] mevalonic acid. The result showed that the intramolecular cyclopropanation reaction is suprafacial on the *re-re* face of the C14-C15 double bond of GGPP. Assuming a carbocation mechanism and inversion of stereochemistry at C1, one can characterize the cyclopropanation reaction as Markovnikov addition-syn elimination. The stereoelectronic assumption about the stereochemistry of cyclopropanation predicts that the *pro-S* proton at C1 is located on the incipient three membered ring when the initial macrocyclic carbocation is formed (Scheme IV).[11] Casbene seems to be a key intermediate in the biosynthesis of other diterpenes which have *gem*-dimethylcyclopropyl groups. There include phorbol, ingenol, and jatropholone-B. Similarly, bicyclogermacrene is an intermediate in the formation of the sesquiterpenes, maaliol and aromadendrene.[6, 8]

Scheme IV



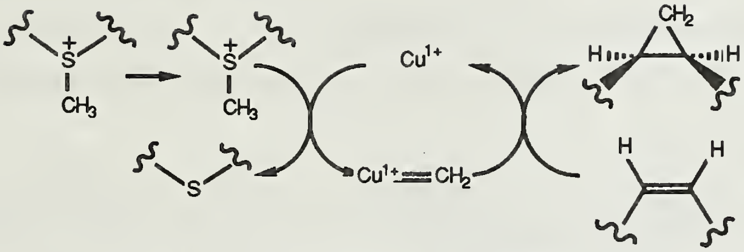
The cyclopropane ring in presqualene pyrophosphate (**19**), an intermediate in the biosynthesis of squalene from farnesyl pyrophosphate (FPP), is considered to be formed by intermolecular cyclopropanation. Based on the absolute configuration and labeling studies with (3R,5R)-[4-^{14}C, 5-^{3}H]mevalonate and (3R,5R)-[5-^{2}H]mevalonate, Poulter and Rilling proposed that C1 of one molecule of FPP is added to the (2-*re*, 3-*si*) face of the double bond of a second molecule of FPP with loss of one of the PP residues and inversion at C1 of the donor. Ejection of *pro-S* hydrogen completes the cyclization as shown in Scheme V.[4c] Prephytoene[12] and chrysanthemol[13] are also believed to have the same biosynthetic pathway from GGPP and GPP, respectively.

Scheme V



This type of cyclopropanation is usually explained by addition of a carbocation to a double bond followed by 1,3-elimination. However, there is still uncertainty as to whether the reaction actually proceeds through a carbocation or a carbenoid intermediate (Scheme VI).[14] It is difficult to differentiate these two mechanisms unless a purified enzyme can be used to study the biosynthesis.

Scheme VI



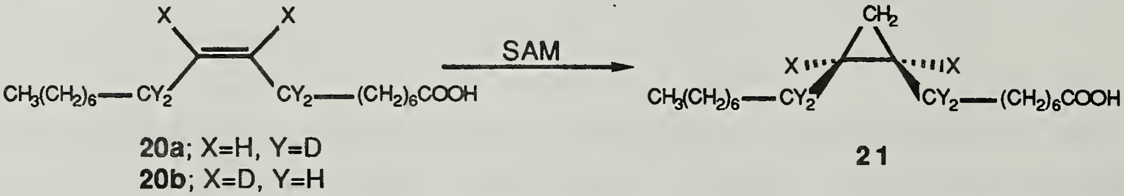
Although 3-carene has been presumed to be formed by 1,3-elimination, the result of biosynthetic studies showed a migration of the double bond with an unusual 1,2-proton shift to the site of the original double bond.[4a] Since these results are accompanied by a controversial proposal about the isomerization between geraniol and nerol via a redox process, this biosynthetic study should be reexamined, preferably with purified enzyme. Sesquicarene,[15] the naturally occuring C15 analog of 2-carene, is also expected to be produced by 1,3-elimination without double bond migration.

Cyclopropanation with S-Adenosylmethionine

The cyclopropane and cyclopropene ring in fatty acids has been known to be formed by the addition of a one carbon unit derived from methionine across the double bond of the corresponding olefinic fatty acid.[16] Labeling studies of cyclopropene containing fatty acids have shown that they are not produced by cyclization on the acetylenic acid, but instead by dehydrogenation from the corresponding cyclopropane fatty acids.[16] In the biosynthesis of dihydrosterculic acid from deuterium labeled oleic acid **20a**, any mechanism involving an allylic proton was ruled out because there was no loss or scrambling of deuterium (Scheme VII).[17] There was no loss or scrambling of deuterium either in dihydrosterculic acid derived from **20b** which suggested that no equilibration of edge or corner-protonated cyclopropyl cation species had occurred.[17] In a ($^2H_3$)-SAM feeding experiment, a significant amount of monodeuterated cyclopropane fatty acid was produced along with dideuterated species.[17] Reversible sulfur ylide formation prior to methylene transfer is a possible way to account for the proton exchange. However, methionine re-isolated from the intercellular pool did not contain any exchanged species.[18] In addition, it has never been shown that cyclopropane synthase is a metalloenzyme,[17, 19] although the original proposal by Cohen *et al.* requires a transition metal carbenoid.[14]

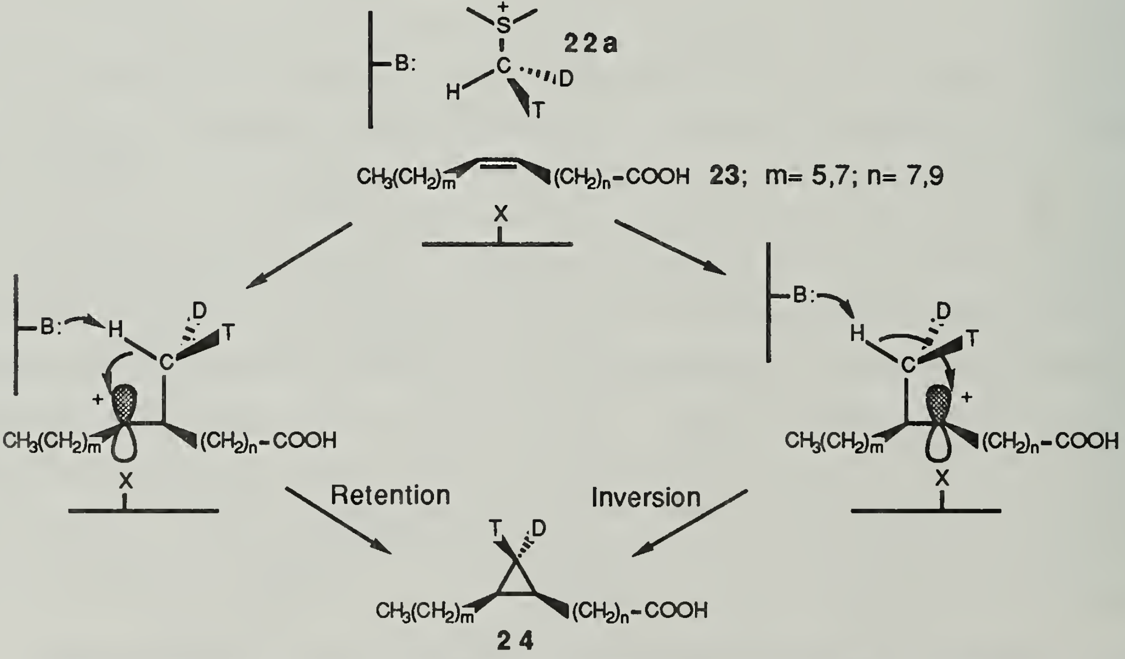
An other possible interpretation for the exchange of a proton is that it occurs in the initial carbonium ion and that the ring closure is reversible. It was found that the rate of cyclopropanation decreased significantly in a 12-fluorooleic acid feeding experiment, which provides evidence for the development of a positive charge on C9 or C10.[20] In addition, a typical intramolecular isotope effect for carbocation mechanism, a negligible intermolecular isotope effect, and an increase of cyclopropane fatty acid content with decreasing pH are also easily understood in terms of a carbonium ion mechanism.[18, 21] Although Cohen's carbenoid mechanism cannot be ruled out completely, these results support a carbocation mechanism in which a methyl group is transfered in a slow step followed by a fast, partially reversible protonation-deprotonation step.

Scheme VII



In the biosynthesis of cyclopropane fatty acids with S-adenosylmethionine (SAM) bearing a chiral methyl group **22a**, Obrecht found that the cyclopropanation of vaccenic acid (**23**, m=5, n=9) gives predominently the doubly labeled lactobacillic acid (**24**, m=5, n=9) with (*R*)-configuration at the introduced methylene group.[19] Based on the carbocation mechanism, this result indicates that the deprotonation of the cation formed by the alkylation of **23** proceeds stereospecifically toward the methyl terminus of the fatty acid carbon chain as shown in Scheme VIII.

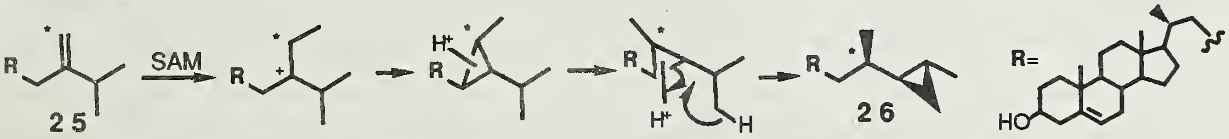
Scheme VIII



Sterols with side chains having more carbon atoms than the cholesterol side chain are found in plants and in many marine organisms. The extra alkyl substituents in the sterol side chain which may include a cyclopropane ring, are derived from SAM methylation of the double bond.[22] Unlike the case of the cyclopropane containing fatty acids, the cyclopropane rings in the sterol side chain are produced after a complicated series of rearrangements, probably through protonated cyclopropane cations. As an example, feeding of [28-^{14}C]-24-methylenecholesterol (**25**) to

Petrosia ficiformis produced petrosterol (**26**) which is labeled at C24 position as shown in Scheme IX.[23] The proposed mechanism which explains this unprecedented result involves SAM biomethylation on the double bond followed by a complex series of rearrangements.

Scheme IX

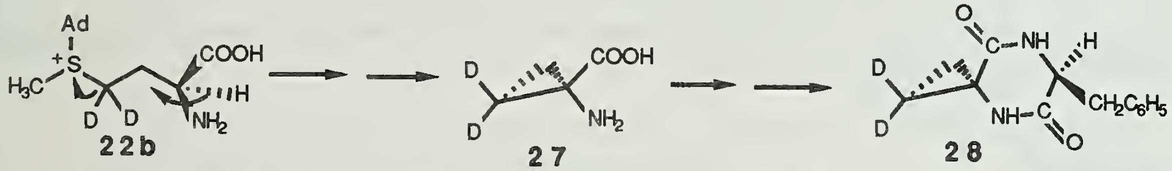


Cyclopropane Ring of 1-Aminocyclopropanecarboxylic Acid

1-Aminocyclopropanecarboxylic acid (ACC) is an unusual amino acid which has been shown to be a key intermediate in ethylene biosynthesis. Adams and Yang proposed a reasonable mechanism for the biosynthetic formation of ACC in which methionine is activated to SAM by ATP and SAM then reacts with pyridoxal phosphate to produce a Shiff's base which extrudes 5-methyl-5-thioadenosine to form ACC.[24]

The substrate stereoselectivity of ACC synthase is such that only the naturally occurring SAM which has (*S*)-configuration at both the sulfur and the α-carbon of the amino acid acts as a substrate.[25] The stereochemical route of ACC formation was also elucidated by feeding a precursor labeled regiospecifically with deuterium in the γ-position.[26] Biosynthesized ACC (**27**) was chemically transformed to dioxopiperazine (**28**) and its ^{2}H-NMR spectrum showed that the ACC generated from deuterated precursor possessed the (*S*)-configuration as shown in Scheme X. Thus it was concluded that the initial alkylation reaction which takes place at the α-carbon atom of the substrate represents an inversion process.

Scheme X

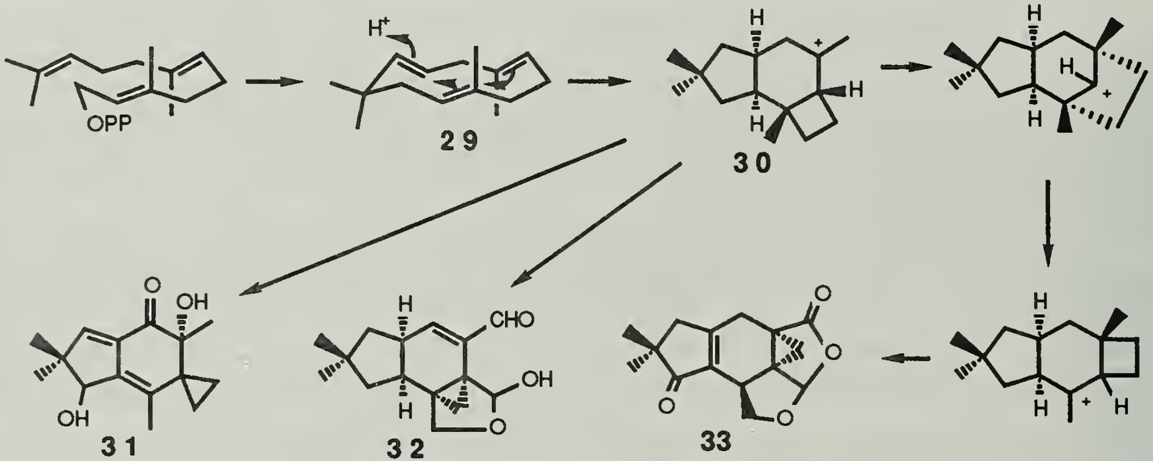


There are some natural products which have an ACC moiety but their biosynthesis may not be similar to that of ACC. In the case of coronatine, the cyclopropane moiety is derived from L-isoleucine.[27] The mechanism of this reductive cyclopropanation has not yet been proposed. Carnosadine is a guanidinomethyl substituted ACC but its biosynthesis has not been reported either.[28]

RING CONTRACTION FROM CYCLOBUTYL CARBOCATIONS

Another cyclopropane ring forming process postulated for the biosynthesis of natural products is ring contraction from a cyclobutyl carbocation. The biosynthetic pathway of illudin M (**31**) and illudin S has been postulated to proceed through the cyclization of *trans, trans*-FPP to humulene (**29**) followed by further cyclization to **30**. This cation then undergoes rearrangement from a 4-membered ring to a 3-membered ring as shown in Scheme XI.[4b] By ^{13}C-NMR analysis of **31** derived from [1,2-$^{13}C_2$]acetate, it was shown that a methylene group in the cyclopropane ring migrated from C-4 is *trans* to C-2 hydroxyl group in **31**.[4b, 29] The unsolved problem in this analysis is that an unprecedented *trans*-1,2-Wagner-Meerwein rearrangement is required in order to satisfy this stereochemistry.[4b] Marasmic acid (**32**)[4b] and sterepolide (**33**)[30] have also been suggested to be produced by series of 1,2-Wagner-Meerwein rearrangements of **30**.

Scheme XI



A cyclopropane sliding process has been proposed in the biosynthetic scheme of some natural products and has been shown to occur chemically in the studies of several irregular sesquiterpene formations such as widdrol,[31] capnellene,[32] and dactylol.[33] In addition, the biogenetic scheme of hybridalactone, a novel eicosanoid, has been proposed to involve a cyclopropane sliding process to result ultimately in a 3-membered ring through ring contraction based on its absolute stereochemistry.[34]

SUMMARY

Enzymatic cyclopropanation occurs mainly by homoallylic to cyclopropylcarbinyl cation rearrangements or by 1,3-eliminations and is rationalized by the cationic mechanism except in the case of ACC biosynthesis. Although the alternative carbenoid mechanism has not been rigorously excluded, the biosynthetic studies of fatty acids support the carbocation mechanism. The reductive cyclization of amino acids to the substituted ACC has not been elucidated clearly.

Although biosynthetic studies have been done on the mechanism and stereochemistry of enzymatic cyclopropanations, there are many cyclopropane-containing natural products whose biogeneses are not yet clear. Biosynthetic studies of these compounds are needed to clarify the cyclopropanation mechanism.

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THE TRIFLUOROMETHYL GROUP: ITS ROLE IN BIOACTIVE MOLECULES AND SYNTHETIC METHODS FOR ITS INCORPORATION

Reported by Mitchell L. Kurtzweil November 28, 1988

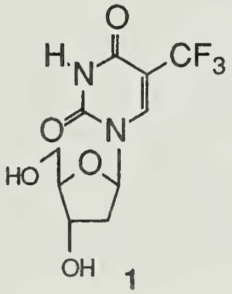
The fact that the trifluoromethyl (TFM) group influences biologically active molecules has drawn increased attention since the introduction of commercial compounds containing this group over thirty years ago. The problem of incorporating the TFM group into molecules in an efficient and economical manner has been a challenging matter during this time. The role of the TFM group in a number of representative bioactive molecules and new ways to add the TFM group to a molecule will be covered in this abstract.

Because the van der Waals radius of the TFM group at 2.44 Å is only slightly larger than a methyl group at 2.00 Å the TFM group[1] can usually be substituted for a methyl group without disturbing the steric effects of the system a great deal. However, because of its strong electron-withdrawing power the TFM group can change the electronic distribution in a molecule and affect the acidity or basicity of neighboring groups, the polarity, and the overall stability and reactivity of nearby functional groups. The C-F bond is also stronger than a C-H bond by up to 20 kcal and this imparts a high degree of stability to the TFM group, making it less susceptible to oxidation and thermally more stable than a methyl group. The TFM group is therefore usually stable to metabolic transformations. Another important factor in biological studies is that the TFM group is among the most lipophilic of all substituents. This generally leads to molecules with enhanced rates of absorption and transport *in vivo*.[2a, b] A final matter to note is that TFM group containing molecules are generally more volatile than their non-fluorine containing counterparts due to lack of intermolecular hydrophobic interactions. This factor is especially important for anesthetics.[3]

BIOACTIVITY BASED ON STERIC EQUIVALENCE

5-Trifluoromethyl-2'-deoxyuridylate (CF_3dUMP)

The nucleoside CF_3dUMP, 1, an equivalent of thymidylate, was first reported by Heidelberger and co-workers in 1962.[1] This compound has been found to show antitumor and



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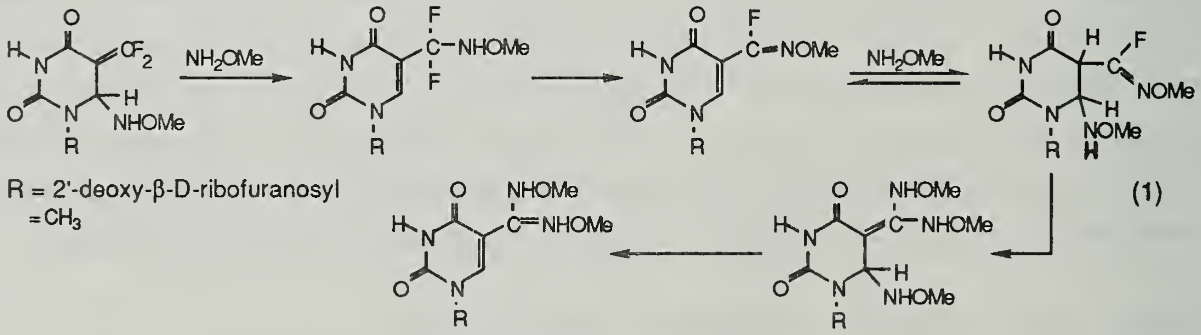
antiviral activity as a result of the inhibition of thymidylate synthase (TS).[4] Because of this a great deal of effort has been made to understand the mechanism behind this inhibition by CF_3dUMP.

Because substitution at the 5-position of dUMP by Br or I led to incorporation into DNA, Heidelberger reasoned that perhaps replacement by the "isosteric" TFM group would yield similar results. Their synthesis, which incorporated the TFM group in the first step by the use of trifluoroacetone, proceeded in rather straight forward fashion to give 5-trifluoromethyl uracil in eight steps. The nucleoside was then prepared enzymatically by an exchange reaction between thymidine and the trifluoromethyl uracil.[1]

Based on findings that CF_3dUMP would acylate amines it was initially proposed that TS was inactivated by nucleophilic attack of an amino function on the enzyme on the TFM group to give a carboxamide.[5] In order to explain this unexpected result additional chemical studies on CF_3dUMP have been carried out. The results of these studies appear to refute direct nucleophilic attack on the TFM group and strongly support initial attack at the 6 position by TS to generate a highly reactive difluoromethylene species at the 5 position.

A rate study done with CF_3dUMP and methoxyamine gave a rate equation of the form, $k_{obs} = k_1[NH_2OMe]_T + k_2[NH_2OMe]_T{}^2$. This is consistent with a mechanism such as that shown in equation 1 which involves a reactive difluoromethylene intermediate.[6] Precedent for this type of mechanism has been shown previously in which several TFM containing molecules could be activated toward fluoride elimination followed by the addition water or hydroxide to yield the corresponding carboxylic acid.[7]



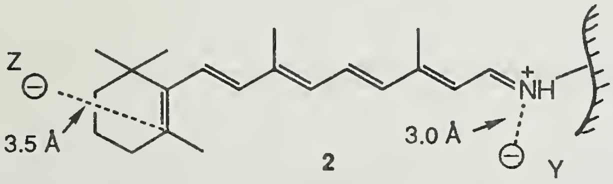
(1)

Additional evidence for attack at the 6 position is provided by the fact that CF_3dUMP also inactivated TS in the absence of the cofactor. This was accompanied by concommitant generation of fluoride ion and the formation of two products, one of which was formed at a faster rate than the other. The product which formed faster was stable to aqueous base, but was converted into the other product by acid. In turn, this product was converted into 5-carboxy dUMP by base.[6] Efforts to assign structures to these products are currently being studied.

BIOACTIVITY BASED ON CHANGES IN ELECTRONIC DISTRIBUTION

Vitamin A analogues

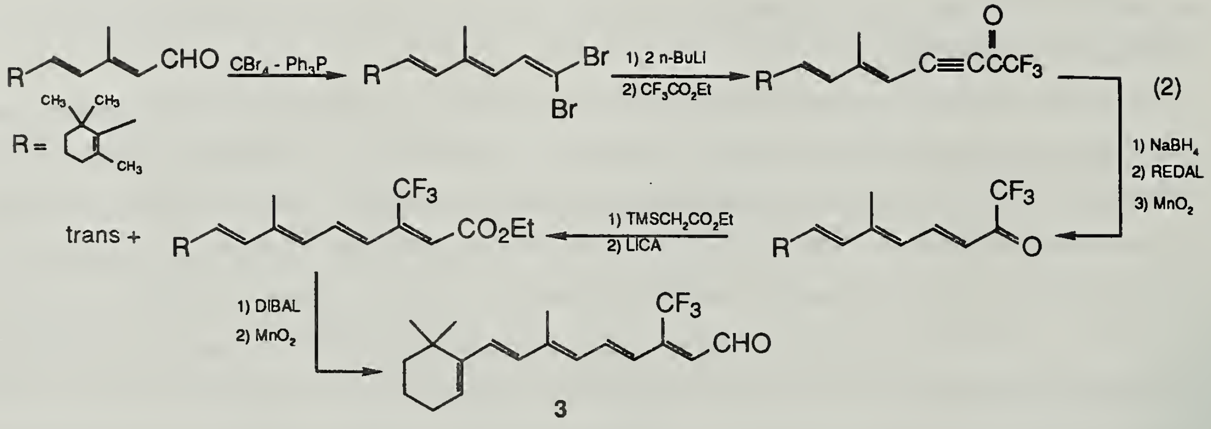
The chromophores known as retinals have received a great deal of attention in recent years. 11-*cis* Retinal is responsible for vision in vertebrates while 11- *trans* retinal is responsible for the conversion of light into a proton pump that is coupled to ATP synthesis in the membrane of *Halobacterium halobium.* Of these two, the *trans* form has been studied the most. It is known that 11-*cis* retinal binds with the terminal amine functionality of a lysine residue in rhodopsin to form an 11-*trans* protonated Schiff base known as bacteriorhodopsin (bR). This imine absorbs light at a wavelength that is red-shifted from an analogous protonated Schiff base formed from n-$BuNH_2$. Efforts to explain this phenonenon have resulted in what is known as an external point-charge model, **2**, in which it appears that the wavelength shifts are induced by an external negative charge, Z, which is located about 3.5 Å from the 5 position of the chromophore within the active site.[8] This model is also supported by theoretical and experimental results which show that a carboxylate anion in the vicinity of either the protonated Schiff base or as part of the conjugated system induces a shift in absorption.[9]



2

Studies to determine how the location of this charge affects the wavelength of absorption without disrupting the steric effects of the system have led to use of the TFM group. In this approach the electronic distribution at various positions within the molecule is changed as a result of the TFM group. This can then be related to the location of charge in the light activated molecule. Equation 2 shows a typical preparation of the 13-*cis*-TFM retinal, **3**, in which the TFM group is incorporated through the use of ethyl trifluoroacetate.[10] The 5-TFM analogue, **5** (eq 3), likewise involves a multi-step synthesis.[11] However, the TFM group is incorporated in the starting material which must then be cyclized through a series of 6 steps to give **4**. Another series of 6 steps then affords **5**.

Studies show that **3** retains its normal proton pumping ability after incorporation into rhodopsin and exhibits an opsin shift which is similar to that found for the natural retinal.[12] This provides further evidence that the negative charge at Z is located near the 5 position.[13] On the other hand, studies show that **5** exhibits a low opsin shift and an inability to pump protons in the photochemical cycle. This suggests that the chromophore is not properly locked in the natural binding site and therefore is not influenced by the external negative charge.[14]



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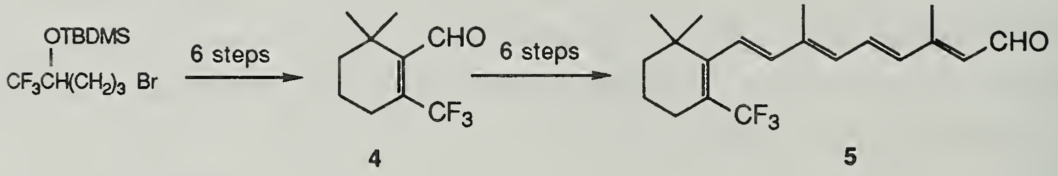
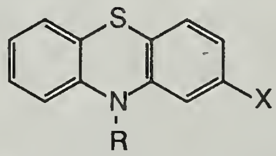


(3)

BIOACTIVITY BASED ON LIPOPHILICITY

Phenothiazines

The use of phenothiazines, whose general formula is shown in **6**, have occupied a large part of the market of neuroleptics for the treatment of patients with mental disorders since the introduction of chlorpromazine (**6a**) in 1954. It was found that by replacing the Cl with a TFM group biological activity was increased 100 fold. The most effective substituents for increasing activity have been found to be when X= CF_3 or CF_3SO_2 and based on these findings a study



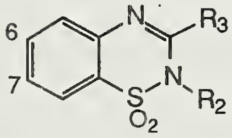
6a, X = Cl, R =$(CH_2)_3NMe_2$

b, X = CF_3, R =—N N$(CH_2)_2$OH

was done to determine whether strongly electron-withdrawing substituents would increase neuroleptic activity.[15] It was initially thought that an electron-withdrawing group would decrease the susceptibility of sulfur toward oxidation, which results in a drastic reduction of neuroleptic activity, possibly as a result of increased water solubility. However, based on the observed results it appears that other parameters besides the electron-withdrawing power of the group are important and it was proposed that the differential lipid-water solubility is probably an important factor.[16]

Benzothiadiazines

The 2H-1, 2, 4-benzothiadiazine 1, 1-dioxides, for which a general formula is shown in **7**,



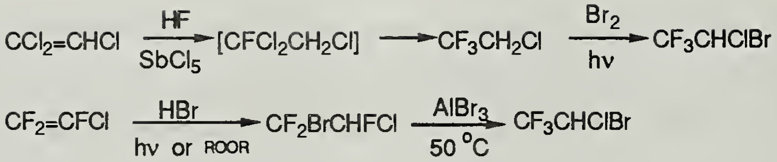
7

show antihypertensive activity while their reduced analogues show diuretic activity and several have proven to be very useful at the commercial level.[17] A series of structure-activity relationships done with benzothiadiazines has shown that substitution with a TFM group at the 6 position generally gives increased activity as evidenced by a marked decrease in blood pressure for periods of one hour or more. Substitution at the R_3 position by a methyl group substantially increased the activity as did other alkyl groups. However, substitution with the TFM at the R_3 position showed no activity.[18] This was attributed to the fact that this compound is > 99.9 % ionized at the pH under which the reaction is run. A treatment of the series of compounds using the substituent constant approach developed by Hansch showed a great dependency on the hydrophobic parameter π values at the 6 and 7 positions while the dependence on π at the 3 position was parabolic in nature. Therefore, if a strong dependence on lipophilicity is necessary for activity it is not surprising that the compound in which $R_3 = CF_3$ is inactive. From these data it was then possible to infer a drug-receptor interaction for which the importance of hydrophobic interactions occur at regions adjacent to the 6, 7 , and 3 positions of the molecule.[19]

BIOACTIVITY BASED ON LIPOPHILICITY AND VOLATILITY

Anesthetics, halothane

The bioactivity of halothane, which is synthesized by either of two methods as shown in equation 4, is the result of a combination of factors.[20] Halothane contains the TFM group and is a small molecule so it has a high degree of volatility. It also contains a single hydrogen which has been suggested to be important in developing hydrogen bonding interactions in the blood. It is known that the time it takes to transport an effective amount of anesthetic to the brain depends on the time taken for the partial pressure of anesthetic in the blood to equal that in the inhaled mixture of anesthetic with air or oxygen. These characteristics account for what is described as the lipid/gas partition coefficient. Studies by Davies and co-workers have shown that a correlation exists between the lipid/gas partition coefficients of volatile halogenated hydrocarbon and their hydrogen bonding capabilities.[21] Similar correlations of the potency of gaseous anesthetics with



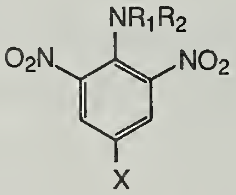
(4)

hydrophobicity and a polar factor have been demonstrated by Hansch.[22]

BIOACTIVITY BASED ON MULTIPLE FACTORS

Dintroanilines

The use of trifluralin, **8a**, for the control of grasses and some broadleaf weeds has made it one of the most widely used herbicides since its introduction in 1960. Trifluralin is synthesized in 3 steps from para-chloro benzotrifluoride which is then dinitrated at the positions ortho to Cl. This is followed by nucleophilic attack of an amine on the activated Cl.[23] Although trifluralin contains the TFM group it does not appear to be necessary in all cases to maintain a high level of control on weeds especially if other analogues show higher crop safety. Research has shown that the primary mode of action in dinitroanilines is on mitotic cell division which results in plant root growth inhibition. While little is known about the actual mechanism of this inhibition it has been shown that the TFM group is stable to metabolic transformations. It also appears that trifluralin is more toxic to plant shoots than an equally active analogue, nitralin (**8b**), which is more toxic to plant roots. It has been suggested that this could be due to the fact that trifluralin is more volatile than nitralin because of its TFM group. It should also be noted that trifluralin has an extremely low water solubility mainly due to the TFM group while nitralin has a hydrophilic SO_2CH_3 group. Because trifluralin often shows higher activity in weeds than its analogues, there is reason to believe that the lipid content of certain plants has an effect on its activity due to its lipophilicity.[24, 25]

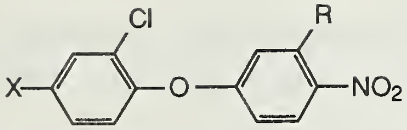


8a, $X = CF_3$, $R_1 = R_2 =$ n- Pr (trifluralin)
b, $X = SO_2CH_3$, $R_1 = R_2 =$ n-Pr (nitralin)

Diphenyl ethers

The diphenyl ethers, **9a-d**, have been found to be potent herbicides for the control of weeds in rice and soybean crops and several are used commercially. It has been found that a 10-fold increase in activity is seen for **9b** in which the TFM group is substituted for the Cl in **9a**.

The synthesis of diphenyl ethers is fairly straightforward and two general methods can be



9a, X = Cl, R = H (nitrofen)
b, X = CF_3, R = H
c, X = CF_3, R = $COO^- Na^+$ (acifluorfen)
d, X = CF_3, R = OEt (oxyfluorfen)

used. In one a para-chloro benzotrifluoride which is activated toward nucleophilic displacement is coupled with a meta-substituted phenoxide in sulfolane at 140 °C for several hours. The resulting ether is then selectively nitrated para to the ether linkage to give the compound, **9d**.[26] Another method involves the coupling of 3-methyl-4-nitro phenol with the same benzotrifluoride in dimethylacetamide at 150 °C for 4 hours followed by sodium dichromate oxidation to give the carboxylate, **9c**.

Studies to determine a structure-activity relationship series with these compounds have been relatively difficult because it has been found that diphenyl ethers act as herbicides by three main routes which include, inhibition of photosynthetic electron transport, energy transfer inhibition, and peroxidative destruction of chloroplast components. However, from one study it was concluded that ligands in the 2 and/or 4 positions of the ring without the nitro group had higher Hammett σ_p parameters generally enhanced herbicidal activity in cases where a peroxidative route dominated.[27]

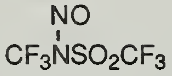
NEW METHODS TO INCORPORATE THE TFM GROUP IN ONE STEP

Most of the methods available to the chemist for introduction of the TFM group into a molecule involve multistep procedures *vide supra*. Recently there has been an increase in the number of new and general methods for its direct incorporation. Since the TFM group has useful biological properties these methods will presumably be used in future synthesis of biologically active molecules.

Perhaps the most emphasis in the development of new TFM containing reagents has been directed toward the CF_3Cu reagent. First reported in 1969, this reagent allows regioselective incorporation of a TFM group upon coupling with an alkyl or aryl halide.[28] The formation of CF_3Cu is readily accomplished by shaking CF_3I along with Cu powder in HMPA at 120 °C for 2.5 hours followed by removal of the excess Cu by filtration.[29] Efforts directed toward the use of more readily available and easier to handle materials have resulted in the preparation of the CF_3Cu reagent from Freon precursors as shown in equation 5. Coupling of the reagent formed in this manner with alkyl or aryl halides generally gave yields in the 80-100% range as determined by ^{19}F NMR.[30]

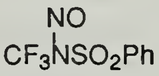
$$\underset{\substack{M = Cd,\, Zn \\ X = Br,\, Cl}}{2M + 2CF_2X_2} \xrightarrow[RT]{DMF} [CF_3MX + (CF_3)_2M] \xrightarrow[Y = I,\, Br,\, Cl]{CuY/\text{-}80\ ^{\circ}C\text{-}RT} CF_3Cu \qquad (5)$$

Another method for introduction of the TFM group has come with the development of compounds N-trifluoromethyl-N-nitrosotrifluoromethane-sulfonamide, **10**, and N-trifluoromethyl-N-nitrosobenzenesulfonamide, **11**, known as TNS-Tf and TNS-B respectively. These reagents act as TFM radical sources and react with aromatics to give TFM containing compounds in moderate to good yield.[31a, b]



$CF_3N(NO)SO_2CF_3$

10



$CF_3N(NO)SO_2Ph$

11

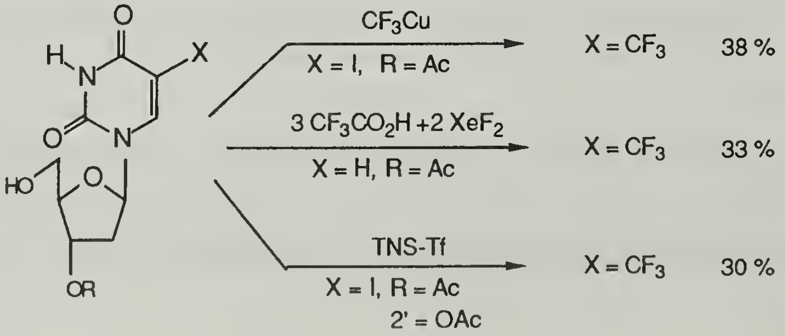
Recently, a TFM reagent which uses trifluoroacetic acid and XeF_2 has been reported (eq 6). The TFM group is also presumed to be transferred to aromatic compounds via a radical species

$$ArH + CF_3CO_2H + XeF_2 \longrightarrow ArCF_3 + CO_2 + Xe + 2HF \qquad (6)$$

and gives moderate isolated yields of the corresponding TFM containing product. Unfortunately, this reagent suffers from a lack of regioselectivity in many cases and it requires the use of the expensive XeF_2.[32]

Because of continuing interest in CF_3dUMP analogues, it should also be noted that several of these aforementioned reagents have been reacted with dUMP analogues to give the desired TFM nucleoside in moderate yields (eq 7).[29, 31b, 32]

Another new approach to introduction of the TFM group which has not been as thoroughly studied is the flash thermolysis of aryl-trifluoroacetates in which the starting material is passed through a quartz tube at 600-700 °C and 10 mm pressure.[33] The major drawback of this method apart from the fact that it requires the use of such harsh conditions is that yields of benzotrifluoride products are low (<25%) and that trifluoromethoxy side-products generally accompany the desired



(7)

products in yields of up to 22%. Perhaps if a catalyst could be developed so that lower reaction temperatures could be used this could become be a viable route to TFM containing molecules.

CONCLUSION

From the information presented it can be seen that the TFM group containing compounds can often show highly favorable bioactive behavior depending on their modes of action. The TFM group has also been used to help gain a better understanding of the active site in biological interactions and to shed further light on a mechanistic sequence of biological events. New methods for the incorporation of the TFM group are also available and may be useful for future syntheses.

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TRIPLET EXCIMERS:AN INVESTIGATION OF THEIR EXISTENCE

Reported by Ji-In Kim December 1, 1988

INTRODUCTION

An excimer is a collision complex formed when an excited molecule, M* collides with a ground state molecule, M.[1] This may be illustrated simply as $M^* + M \longrightarrow (MM)^*$. The excimer is a complex which is stable in the excited state but unstable in the ground state. The excited state species can be seen as a polarizable species with a half-filled electrophilic HOMO and a nucleophilic LUMO. These half-filled orbitals may participate in a favorable charge-transfer type interaction with other polarizable species.[2] This interaction is shown in Fig. 1 in a potential energy diagram for the formation of excimer .

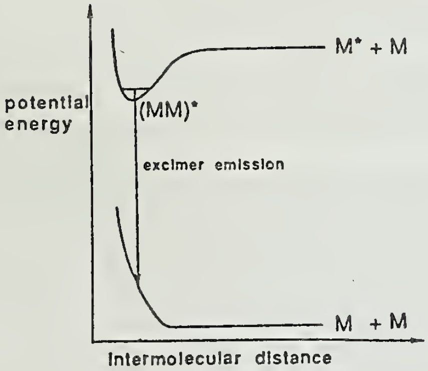

Figure 1. A schematic diagram of the potential energy as a function of the intermolecular separation.

The first experimental evidence for an excimer was reported by Förster and Kasper for pyrene in n-heptane solution.[3] They detected a new, red-shifted emission in the fluorescence spectrum which grew in intensity with increasing pyrene concentration. This emissive component was attributed to a singlet state excimer. Since then, thousands of singlet excimers of aromatic compounds in liquid solutions have been detected. As a result of the existence of singlet excimer, the possibility of triplet excimer has been studied and efforts have been made toward the detection of a triplet excimer. However, no conclusive evidence for the triplet excimers has been found.

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PHOTOPHYSICS

The following experiments have been carried out to characterize singlet excimers of pyrene in solution. Similar evidence has been found for other singlet excimers of aromatic hydrocarbons in solution.

a) The fluorescence spectra of pyrene at room temperature in non-polar solvent, n-heptane, were recorded at various concentrations. At concentrations of less than 5×10^{-5} M, the fluorescence spectra were that of monomeric pyrene but at higher concentrations, a new, structureless fluorescence emission grew in at a longer wavelength .[4] However, there was no change in the absorption spectrum with the concentration change, indicating that ground state complex formation and stable photoproducts are not responsible for the change in the emission spectrum. Therefore, the new fluorescence was attributed to an excited-state complex.

b) The rise and decay time of the monomer and excimer fluorescence of pyrene were measured in cyclohexane using time-resolved emission spectroscopy.[5] Upon direct excitation, a time delay was observed between the fluorescence maxima of the monomer and the excimer. This indicated that the excimer formation is time dependent. In order to determine if the excimer formation process was diffusion-controlled, the value of the activation energy of excimer formation for pyrene was determined and compared with the theoretical value of the activation energy of collisional complex formation. This theoretical value was evaluated from the viscosity and temperature data for various solvents.[6] In the case where cyclohexane was the solvent, the values were identical (3.2kcal/mole), confirming a diffusion-controlled excimer formation process.

c) The relative quantum yields of excimer and monomer fluorescence, I_D/I_M, of pyrene in solution were measured as a function of temperature.[7] At low temperatures, the limiting values were the rate parameters for the excimer dissociation and internal conversion, whereas at high temperatures, the excimer dissociation rate parameter became large. This indicates that excimer formation predominates at low temperatures but as the temperature increases, the dissociation into monomers becomes more evident due to thermal activation.

The above experimental data and others cited in the literature have been used to show that singlet excimers are formed.[8] However, very little is known about the excimer in its triplet state. Such a species would be very difficult to detect experimentally, in fluid solution by phosphorescence measurement, because the quantum yield of phosphorescence of rigid aromatic compounds is much lower than the quantum yield of fluorescence. This is due to a very weak spin-orbit coupling interaction of the spin-forbidden transition, $T_1 \longrightarrow S_0$.[2] Unfortunately, energy loss, either due to an impurity which could quench the long-lived triplet or to an internal energy conversion, would also reduce the intensity of an already weak phophorescence emission intensity. Due to this weak triplet emission, it is much more difficult to carry out similar experiments for triplet excimer phophorescence as described above. Therefore, the existence of triplet excimers is still under question.

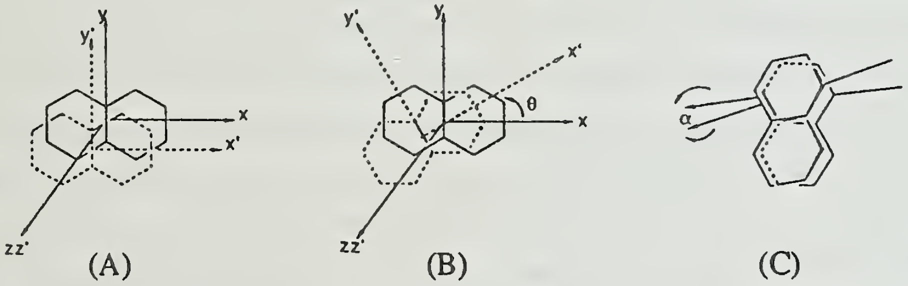
EXCIMER STABILITY-CALCULATIONS

In view of the experimental difficulties, theoretical calculations have been carried out to assess the stability of both singlet and triplet excimers. The calculations were used to predict what combination of forces are responsible for the potential energy of the excimer .

The molecular interaction in the excited state and the origin of the binding energy were explored using a full perturbative approach for the various configurations of the singlet and triplet excimers of naphthalene.[9] In order to simplify the energy calculation for a large aromatic hydrocarbon such as naphthalene, the following approximations are made:

1. The excimers are formed through the lowest-energy transition $\pi\pi^*$.
2. Molecular orbitals below the highest π-orbital are considered a part of the "σ-core". These σ-core electrons are tightly bound so that they do not participate in photochemical processes and the σ-σ interaction in the excimer is the same as in the ground state dimer.
3. Since the σ–π interaction makes only a small contribution to the excimer potential, the σ–π interaction can be neglected.
4. The σ and π electron terms can be calculated separately.

The Hamiltonian of a composite system with V as an interaction operator, can be represented as $H=Hm+Hm'+V$. At the level of zeroth order approximation, the interaction potential of the singlet and triplet excimers of naphthalene includes significant contributions from $\sigma\sigma$- and $\pi\pi$-dispersion energy and exciton resonance. Exciton resonance is the resonance stabilization gained from a dipole-dipole interaction of excited and unexcited molecules. The total interaction energy calculation was also carried out on possible equilibrium conformations shown in Fig.2, as function of tilt angle,α, and phase angle,θ.



(A) (B) (C)

Figure 2. Various conformations of naphthalene. (A) symmetric sandwich conformation (B) rotated sandwich conformation (C) tilted conformation.

Using the one-electron approximation, exciton resonance stabilization is the same for both the singlet and triplet excimers but when using the two-electron approximation, exciton resonance stabilization is much smaller for the triplet excimer than the singlet excimer. This reduced stability is due to an increase in the electron repulsion term caused by two electrons with unpaired spins. The calculated binding energy of naphthalene singlet excimer, with the preferred symmetric sandwich conformation (2A), is 6.9kcal/mole. Birks and his coworkers experimentally determined the binding energy of the singlet naphthalene excimer in cyclohexane by the difference of the activation energies for excimer dissociation and formation.[10] The reported value of 5.8±0.9kcal/mole differed from that of the calculated by 1.1kcal/mole. Using the same method, the binding energy for the triplet naphthalene excimer was calculated to be 1.4kcal/mole, which is 5.5kcal/mole less than that for the singlet excimer. The calculation also predicted that the equilibrium conformation for the triplet excimer is a rotated sandwich complex, as shown in 2B, quite different from the singlet excimer, 2A.

The study concludes that the stability of the singlet excimer comes from both the exciton resonance and dispersion energy terms whereas the conformational difference is primarily due to the exciton resonance term.[9] Since no stabilization is gained from the exciton resonance term for the naphthalene triplet excimer, its calculated potential energy must be similar to that of a ground state dimer whose potential energy comes from the combination of a short-range repulsive interaction and a long-range attractive van der Waal's interaction.[2]

Other semiempirical calculations on the excimer energy of aromatic molecules were based on the configurational interaction of exciton resonance and charge resonance states.[11] The charge resonance stabilization is derived from a Columbic interaction between positive and negative ion molecular states.

In a theoretical study, Lim constructed the naphthalene excimer as a "supermolecule" whose molecular orbitals are combination of the MO's of the monomers.[12] Assuming that the naphthalene excimer has D_{2h} symmetry (Figure 2A) to maximize the π-orbital overlap and assuming orthogonality of HOMO and LUMO coordinates, Hückel-type dimer orbitals are formulated. Lim's energy calculation predicted 27.7kcal/mole of energy difference between the lowest energy levels (0,0 band) of the monomer and the singlet excimer with a given naphthalene sandwich configuration whose interplanar distance is 3A. This calculated value is in good agreement with the experimentally determined value of 28.1kcal/mole.[13]

Lim also calculated that the stability of the triplet excimer with respect to dissociation was +1.6kcal/mole.[14] This was determined by the energy difference between the lowest energy state of the triplet excimer and the repulsion energy of the ground state dimeric molecule using the value of 6.9kcal/mole[5] as the repulsion energy of naphthalene ground state dimer at 3A separation. This result suggests that the triplet excimer state is unstable with respect to dissociation.[14]

In conclusion, both theoretical calculations suggest that triplet excimers are less stable than singlet excimers and as a result, that their formation is less likely.

EXPERIMENTAL RESULTS

The lack of stabilizing forces in triplet excimers, as predicted by the theoretical calculations, may account for the failure to observe excimer phosphorescence of the aromatic hydrocarbons in solution. Therefore, other experimental observations have been used to support the presence of triplet excimers.

One attempt includes a kinetic study done by Hoytink[15] on the lifetimes of triplet species of aromatic hydrocarbons in solution. This study was prompted by an observation that the triplet lifetimes of aromatic compounds in liquid solution was relatively shorter than in a rigid solution. In order to argue that the triplet excimer formation is responsible for the shorter triplet lifetime, the temperature and concentration dependence of the triplet decay time were measured for the aromatic compounds such as naphthalene, anthracene, pyrene, and phenanthrene.

In this study, two important assumptions were made. The first assumption is that the formation of triplet excimer occurs much slower than the diffusion-controlled rate because the "proposed" conformation of triplet excimers is said to have a more specific orientation than singlet excimers,[15] and because the triplet monomer decay constant, k_T, increased with increasing temperature, as usually does in a thermally activated process. The second assumption is that at high temperatures, the triplet excimer formation is less dissociative.

The study concluded that the concentration dependance of k_T for most compounds is from self-quenching to form the triplet excimer, but that the exceptionally high degree of quenching of triplet phenanthrene is due to the presence of impurity in the solution.[15] The study also proposed a kinetic scheme which was previously used to explain the experimental observations for the singlet excimer.[4,16] However, the same scheme failed to explain for the triplet excimers even with numerous assumptions. Thus, Nickel and Prieto reconsidered the data using a slightly different reaction scheme, shown in Scheme I, which includes the formation of a triplet encounter complex, $({}^3M^*\text{--}{}^1M)$:[17]

Scheme I

$$\begin{tikzcd}
{}^3M^* + {}^1M \arrow[r, shift left, "k_{12}"] \arrow[d, "k_1"] & ({}^3M^* \text{--} {}^1M) \arrow[l, shift left, "k_{21}"] \arrow[r, shift left, "k_{23}"] \arrow[d, "k_2"] & {}^3(MM)^* \arrow[l, shift left, "k_{32}"] \arrow[d, "k_3"] \\
M & 2M & 2M
\end{tikzcd}$$

Only a simple assumption of a steady state approximation on the concentration of the encounter complex is made:

For a non-diffusion-controlled concentration quenching;

$$k_T = k_1 + k_{12}(k_{23}/k_{21})(k_3/k_{32})[{}^1M] \qquad (1)$$

and for a diffusion-controlled concentration quenching;

$$k_T = k_1 + k_{12}(k_{23}/k_{23}+k_{21})[{}^1M] \qquad (2)$$

and $K_{12} = k_{12}/k_{21} = N_A v$ (3)

where k_T = triplet monomer decay constant

K_{12} = equilibrium constant for the formation of triplet encounter complex

N_A = Avogadro's number

v = characteristic volume = $(104\pi/3)r^3$

The study contradicts Hoytink's results by concluding that the decay of the triplet excimer is a thermally activated process since experimentally observed triplet decay constant increases with increasing temperature. With increasing temperature, the temperature-independent equilibrium constatnt K_{12} remained the same while the equilibrium constant K_{23} decreased, indicating that k_3 must be increasing thermally. Also, the kinetic analysis in scheme I which uses an encounter complex equilibrium constant, K_{12}, with a characteristic volume term, accounted for the experimentally observed differences in the triplet decay time of phenanthrene. It was also concluded that the new encounter complex involves an "unspecific interaction between ${}^3M^*$ and ${}^1M$ ".[17] Although k_2 is considered small compared to k_{21} or k_3, this is yet another path through which the energy dissipation can occur. Therefore, the presence of this triplet encounter complex as a precursor to the formation of an excimer may also make the formation of the triplet excimer more difficult compared to the singlet excimer.

Baba and coworkers investigated irradiation of aromatic hydrocarbons in a liquid solution of isooctane using phosphorimetry.[18] A new and broad phosphorescence band was observed and it was attributed to the triplet excimer. In addition, the emission maximum around 510nm remained practically independent of the particular solute used.

The triplet lifetime of naphthalene monomer has been obtained from an emission decay study and a value of 1msec has been obtained in contrast to 500msec obtained by Tsai and Robinsosn.[19] Such a discrepency is probably due to the presence of an impurity. Knowing that commercial isooctane does contain a trace amount of strongly phosphorescent diacetyl, photophysical properties of diacetyl were measured. These properties matched convincingly well with the spectroscopic data obtained from the study by Baba. Lastly, when the solvent was purified, the phosphorescence with its emission maximum about 510nm was no longer observed.[17]

The results suggest that the observed phophorescence emission may have been due to an impurity. Thus, it is important to carefully assign the new and structureless emission band since it is uncertain whether it is due to triplet excimer phosphorescence or due to the sensitized phosphorescence from an impurity present. The difficulty in deciding between the two pathways, has been addressed in the literature repeatedly. There have been numerous cases where emission assigned to the triplet excimer of an aromatic hydrocarbon in solution turned out to originate from an impurity[20]. Other examples also have been reported for the detection of triplet excimers in solution, such as halobenzene molecules and 1-chloronaphthalene in isooctane.[21] For these results as well, the possibility of impurity presence cannot be disregarded. The explanation of possible impurity quenching in these experiments is even more convincing, as different purification techniques produced different emission intensities of the new phosphorescence, according to a study by Nickel and Prieto.[17]

In an attempt to irradicate the problem of impurity quenching from triplet excimer formation experiments, intramolecular cases were studied.[22] There are two obvious advantages to the intramolecular model. First, the kinetics of bimolecular and unimolecular quenching will be quite different. For the intermolecular cases, both quenching pathways are bimolecular whereas in the intramolecular case, only the impurity quenching will be bimolecular. Second, for triplet excimer formation in which formation constants or binding energies are predicted to be small, intramolecular triplet excimer formation may be more favorable.

Lim's study included the compounds such as 1,1-di-α-naphthylmethane, 1,2-di-α-naphthaylethane, 1,3-di-α-naphthylpropane, and 1,4-di-α-naphthylbutane, where n=1,2,3,or 4, respectively, as shown in Fig.3.[23] His emission study showed that even at very low concentrations of aromatic hydrocarbons, a red-shifted phosphorescence was observed.[22] This was attributed to the intramolecular triplet excimer. Since intermolecular excimer formation is much more favorable at high concentrations[3] and since an increase in the rise time of excimer phosphorescence is observed with an increasing number of carbons in the chain, the phosphorescence resulting from intermolecular excimer can be ruled out.

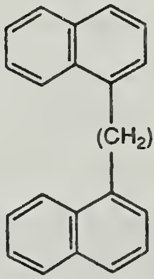


Figure 3. Structure of di-α-naphthylalkanes studied for intramolecular cases where n = 1,2,3, or 4.

Although Lim's results were encouraging, the presence of an impurity which can also phosphoresce could not be ruled out. Assuming that diacetyl-like compounds are the possible impurities, Nickel used a photochemical transformation in an effort to get rid of any impurities responsible for the phophorescence. This transformation exposed the sample to UV irradiation which will not affect the solute photochemically but which will make the impurity into a weakly phosphorescent compound, reducing the intensity of the sensitized phophorescence from the impurity.[24] When the emission spectra were compared, before and after the irradiation, the relative intensity of monomer phosphorescence to the red-shifted phosphorescence changed from 1:5 to 1:2, indicating that the impurity phosphorescence is partially responsible for the observed phosphorescence which was labelled as the triplet excimer emission. Although Nickel and Meyer did not suggest what was responsible for the remaining phosphorescence, the study suggests that even in the intramolecular cases, the observed phosphorescence cannot be labelled correctly as the triplet excimer emission.

SUMMARY

The theoretical calculations indicated that triplet excimers are less stable than singlet excimers and that their stability is similar to that of ground state dimers. The available experimental data, although still conflicting due to the possible presence of an impurity, show a general agreement with the calculations. So far, the spectroscopic evidence for the existence of theoretically possible excimer in its triplet state, have proven inconclusive.

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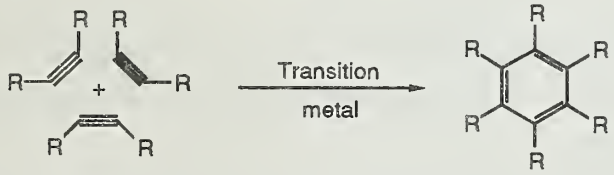
TRANSITION METAL CATALYZED CYCLOTRIMERIZATION REACTIONS: MECHANISM AND SYNTHETIC APPLICATIONS

Reported by Shawn T. Kerrick December 5, 1988

INTRODUCTION

Although Berthelot reported the thermal trimerization of acetylene to benzene in 1866[1] and Reppe et al. used nickel to catalyze the formation of substituted benzenes from substituted alkynes in 1948[2], synthetically useful transition metal catalyzed cyclotrimerizations of alkynes were relatively undeveloped until the late 1970's. A lack of control of the chemo and regioselectivity plagued these reactions until Vollhardt utilized trimethylsilyl substituted acetylenes and a cobalt catalyzed approach. The reaction is a formal [2+2+2] mediated cycloaddition as shown in equation 1 and has the capacity to form a number of bonds and rings in one step. This abstract will detail the mechanisms of this reaction and review the wide variety of synthetic applications of this highly efficient multiple bond forming process.[3,4]



(1)

MECHANISM

Two parallel mechanistic pathways are generally considered to be involved in the catalytic cyclotrimerization of alkynes to benzenes. These are shown in Schemes I and III. A wide variety of metals (M) have been shown to mediate this reaction including Al, Ti, Cr, Nb, Ta, Ru, Fe, Co, Rh, Ir, Ni and Pd.[2,3,5-13] The best metals seem to be the low valent group eight transition metals, although cobalt, in the form of cyclopentadienylcobalt dicarbonyl, has been the metal of choice in most of the synthetically useful applications. A wide variety of subsitituents on the alkyne can be tolerated; these include R=H, alkyl, aryl, vinyl, COR', CO_2R', CH_2OH, CH_2OR', NR'_2, SR',and SiR'_3 groups. Only relatively reactive functionalities such as NO_2 and aryl, vinyl, and alkyl halides interfere with the reaction, presumably due to facile oxidative addition.

The first step of the mechanism shown in Scheme I involves the dissociation of two ligands from complex **1** and subsequent coordination of two alkynes to give the dialkyne complex **4**. The two alkynes then undergo oxidative addition to give the coordinatively unsaturated valence tautomer **5**. This metallacyclopentadiene has a formal oxidation state two units higher than complex **4**. Coordination of the third alkyne molecule gives the alkyne-metallacyclopentadiene

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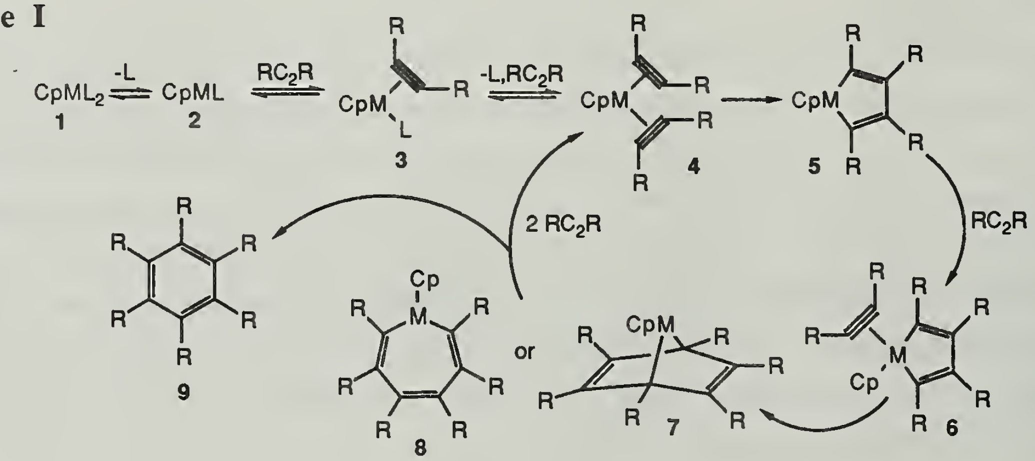
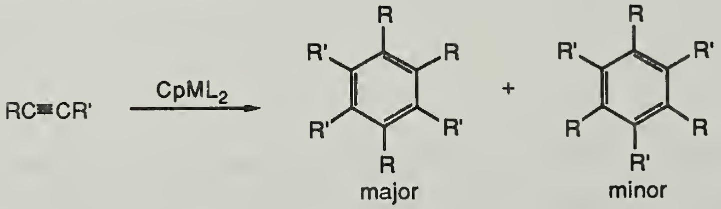
complex **6**. In the next step of the catalytic cycle, **6** is considered to undergo either a Diels-Alder type cycloaddition to give the bridged metallacycle **7** or alkyne insertion into one of the cobalt-carbon bonds to give the metallacycloheptatriene **8**. In either case, reductive elimination of the arene **9** and concomitant release of the coordinatively unsaturated metal complex "CpM" is the final step.

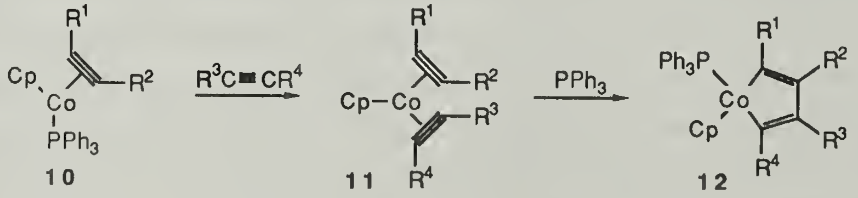
Scheme I



When mono or unsymmetrically substituted alkynes are trimerized as shown in equation 2, the major product is almost always the 1,2,4 regioisomer. The 1,3,5 product is also formed as the only other detectable regioisomer.

 (2)

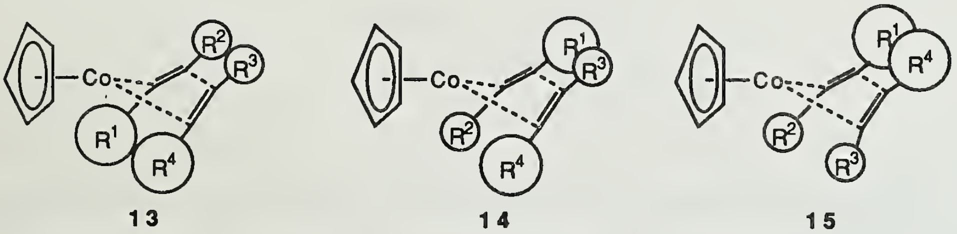
With the hope of determining the origin of this selectivity, Wakatsuki et al. studied the stoichiometric reaction shown in equation 3.^{14} A variety of cobalt complexes **10** were reacted with a number of different alkynes. Displacement of triphenylphosphine produced alkyne complexes **11** which rapidly underwent oxidative addition to coordinatively unsaturated metallacyclopentadienes. Triphenylphosphine then recoordinated to the cobaltacycle to yield isolable complexes **12**.

 (3)

It was shown that these complexes effectively catalyze the cyclotrimerization of alkynes. This indicates that either metallacycle **5** is an intermediate in the catalytic cycle or that complexes **10** and **12** decompose to an active catalyst under the reaction conditions.

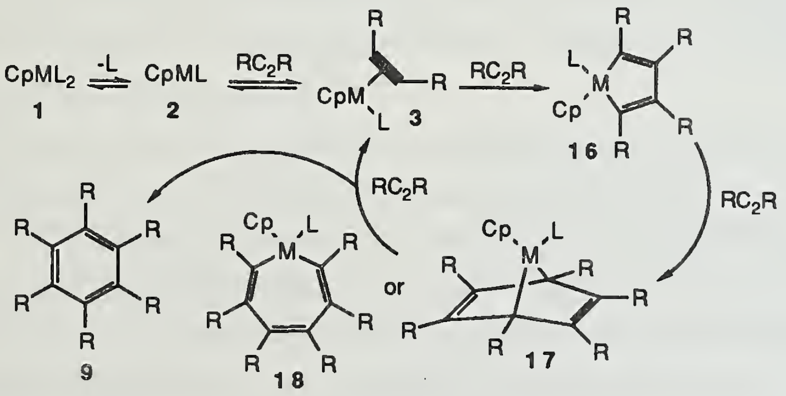
Wakatsuki observed that steric effects controlled the formation of one cobaltacycle regioisomer. For example, complex **10** (R^1, R^2=Ph), when reacted with phenylacetylene, gave exclusively regioisomer **12** (R^1, R^2, R^4=Ph, R^3=H) in 85% yield. A general trend was noted which showed that the sterically most demanding substituents always appeared α to the cobalt in the metallacycle. This observation can be easily explained by consideration of the three possible transition states between complexes **10** and **12** shown in Scheme II. Transition state **13** is clearly preferred over options **14** and **15** based on the steric repulsion encountered between the substituents on the β carbons of the cobaltacycle. This preference for the 2,5-metallacyclopentadiene leads directly to the formation of the 1,2,4 regioisomer upon reaction with a third alkyne.

Scheme II

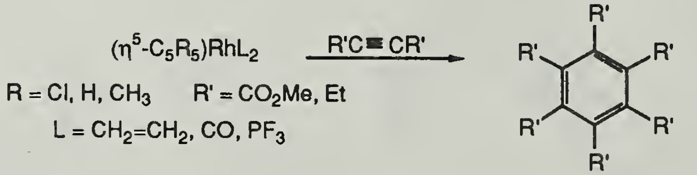


An alternative mechanism shown in Scheme III has the ligand remain coordinated to the metal throughout the catalytic cycle. Addition of a second alkyne results in the direct formation of the metallacyclopentadiene complex **16** without loss of the ligand. The next step involves either a Diels-Alder type cycloaddition to give the bridged metallacycle **17** or a cobalt-carbon bond insertion to give the metallacycloheptatriene **18**. Reductive elimination produces the arene **9** and the coordinatively unsaturated complex **2** in the final step.

Scheme III



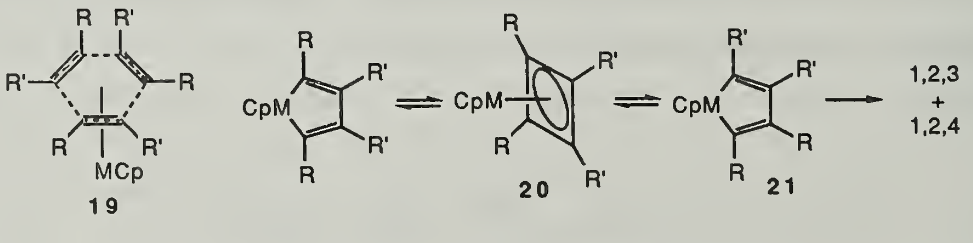
Booth et al. has provided evidence for this alternative mechanism by investigation of the rate of catalytic cyclotrimerization of a variety of alkynes as a function of the ligand on cyclopentadienyl-rhodium complexes as shown in equation 4.[15] They found that both the ligand (L) and the cyclopentadienyl (η^5-C_5R_5) moiety effect the rate of reaction. This would seem to indicate that both the Cp ring and the ligand are bound to the metal during the rate determining step of the catalytic cycle. One way in which the ligand could effect the rate of reaction in Scheme I would be if it could compete with an alkyne molecule for a coordination site on the metal. This is considered unlikely under the catalytic conditions employed in this study in which [alkyne]/[catalyst] > 100/1. Booth also found that electron rich alkynes (R'=Et) were trimerized faster when the catalyst had good acceptor ligands (L=CO or PF_3) and electron poor alkynes (R'=CO_2Me) reacted faster with good donor ligands (L=CH_2CH_2). This would also seem to indicate that the ligand plays a role in the catalytic cycle shown in Scheme III.



(η^5-C_5R_5)RhL_2
R'C≡CR'
R = Cl, H, CH_3 R' = CO_2Me, Et
L = CH_2=CH_2, CO, PF_3
R'
R'
R'
R'
R'
R'

(4)

Some of the alternatives which have been considered for the mechanisms in Schemes I and III involve transition state **19** and intermediate **20** as shown in equation 5. Transition state **19** illustrates a concerted [2+2+2] transition metal mediated cycloaddition. If **19** was involved in the mechanism, the sterically most favorable arrangement of alkynes would give predominantly the 1,3,5 isomer. Since this isomer is usually not the major product, this alternative mechanism seems unlikely.



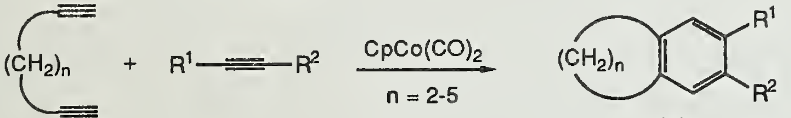
(5)

A second alternative as an intermediate is cyclobutadiene complex **20** as shown in equation 5. Whitesides and Ehmann studied the cyclotrimerization of 1,1,1-trideutero-2-butyne (R=CH_3, R'=CD_3) and found that only the 1,2,4 and 1,3,5 isomers were produced.[16] None of the 1,2,3 isomer could be detected. If complex **20** was an intermediate, then oxidative addition of the cyclobutadiene ligand to give valence tautomer **21** could lead directly to the formation of the 1,2,3 isomer. Since this product is usually not detected, the cyclobutadiene complex **20** is also an unlikely intermediate.

BENZENES AND PYRIDINES

The applications of the reaction of alkynes with transition metals to the synthesis of substituted benzene rings is not practical due to low chemo and regioselectivity. Mono and unsymmetrically substituted alkynes typically give mixtures of the 1,2,4 and 1,3,5 regioisomers in ratios influenced by the steric bulk of the substituents. Jhingan and Maier have recently reported a heterogeneous Pd/C catalyst which can cyclotrimerize symmetrically substituted alkynes in high yield and is particularly effective on a preparative scale.[17] Homogeneous $PdCl_2$ generated in situ catalyzes the cyclotrimerization.

Annelated benzenes have been synthesized from 1,n-diynes and substituted alkynes by Vollhardt as shown in equation 6.[18] Bistrimethylsilylacetylene (BTMSA) proved to be the most synthetically useful alkyne since it is sterically incapable of cyclotrimerization on its own. Even the highly strained benzocyclobutene 22 (n=2; R^1,R^2=$SiMe_3$) was sythesized in 65% yield using this procedure. A wide variety of alkyne substituents could be tolerated, however yields were <50% when BTMSA was not used.



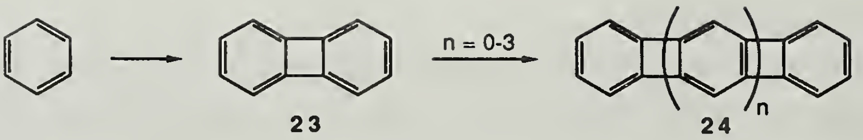
22

(6)

Pyridines can also be synthesized by the cooligimerization of alkynes with nitriles. Wakatsuki et. al found that nitriles gave no reaction with alkyne-metal complexes.[19] However, when alkynes were added to these mixtures, pyridines were formed in good yields. Bönnemann has shown that a variety of 2-substituted pyridines can be synthesized from nitriles and acetylene under pressure in ~90% yield.[20] Vollhardt found that annelated pyridines could be synthesized from diynes and nitriles under high dilution.[21] The main advantage to these methods is the direct formation of the pyridine ring from acyclic precursors. A wide variety of functional groups on both the nitrile and alkyne can be tolerated. The major disadvantage of this synthesis is a lack of control of regioselectivity. This approach to pyridines compares very well to more traditional methods in both yield and steps required.[22]

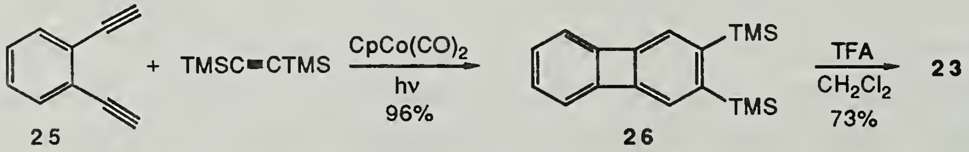
PHENYLENES

Vollhardt, who discovered that highly strained benzocyclobutenes could be synthesized by cobalt catalyzed cyclotrimerization of alkynes, used this approach to synthesize a number of [n]phenylenes 24 (eq. 7).[23] These molecules are of theoretical interest because their π-electron systems alternate between 4n and (4n+2) as each phenyl ring is added. Vollhardt hoped to investigate the unique properties of these highly strained molecules.



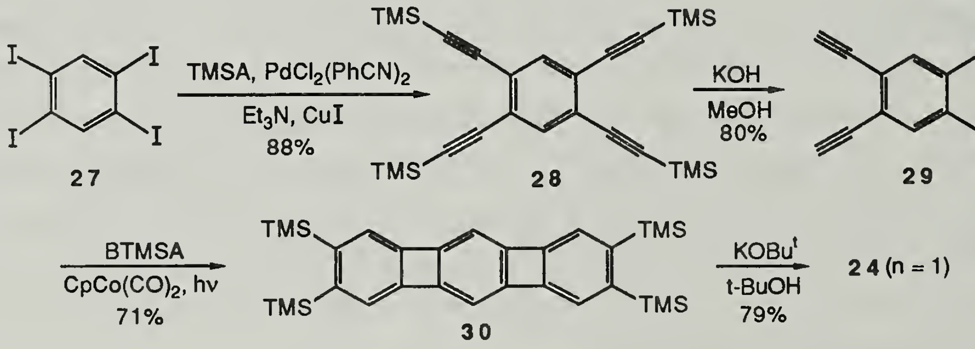
(7)

Biphenylene **23** (n=0) was readily synthesized as shown in equation 8. 1,2-Diethynylbenzene **25** was allowed to react with BTMSA to give 2,3-bis(trimethylsilyl)biphenylene **26** in 96% yield. Protodesilylation with trifluoroacetic acid (TFA) gave a 73% yield of biphenylene **23**. This was the first synthesis of biphenylene in which two of the three rings were made in one step.



(8)

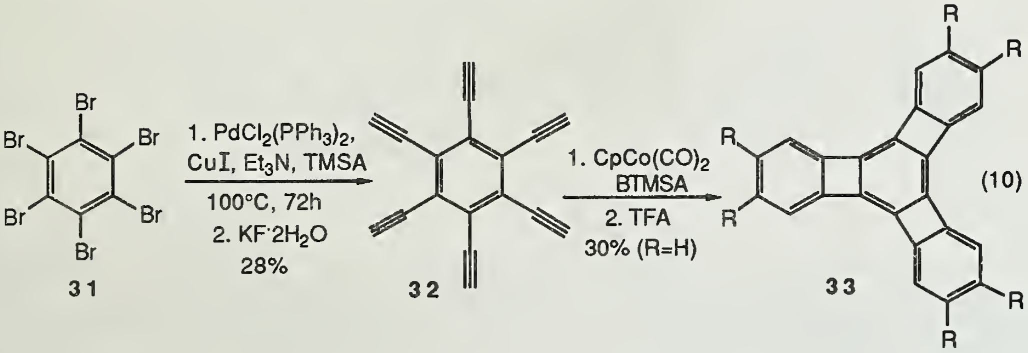
[3]Phenylene **24** (n=1) was similarly synthesized as shown in equation 9. Iodobenzene **27** was converted in one step to tetraalkyne **28** via palladium catalyzed cross coupling with trimethylsilylacetylene (TMSA) in 88% yield. Deprotection of the alkynes with base (80%) followed by cobalt catalyzed cooligimerization with BTMSA gave **30** in 71% yield. Desilylation with potassium t-butoxide produced [3]phenylene **24** (n=1) in 79% yield. In this synthesis, cobalt mediated [2+2+2] cycloadditions selectively formed six bonds and four rings in one step. Previous syntheses of these phenylenes relied on low yielding intramolecular cyclizations.[24]



(9)

Vollhardt has recently extended this general approach to the first reported synthesis of both [4]phenylene **24** (n=2) and [5]phenylene **24** (n=3). The properties of these molecules were very interesting. Spectral analyses indicated that the outer rings in the series **24** (n=0-3) were becoming more aromatic at the expense of the inner rings. This indicates that antiaromatic cyclobutadienoid character is avoided by some degree of bond localization in the inner rings. However, a consistent bathochromic shift in the UV spectra indicated that through conjugation was still occurring.

Perhaps the most interesting synthesis in this series is shown in equation 10.[4] Hexabromobenzene **31** was converted to hexaethynylbenzene **32** (28%) by palladium catalyzed alkyne coupling of TMSA followed by flouride induced desilylation. The triangular [4]phenylene **33** (R=$SiMe_3$) was then synthesized via cobalt catalyzed cooligimerization of **32** with BTMSA (39%). Protodesilylation then gave the phenylene **33** (R=H) in 77% yield. It should be noted that nine bonds and six rings of this extraordinarily strained phenylene were made by cobalt catalyzed cyclotrimerizations. An X-ray structure of **33** (R=$SiMe_3$) clearly showed a high degree of bond localization in the central ring (outer bonds, 1.34Å; inner bonds, 1.49Å), thus yielding a close analog to the theoretical 1,3,5-cyclohexatriene.



31 32 33

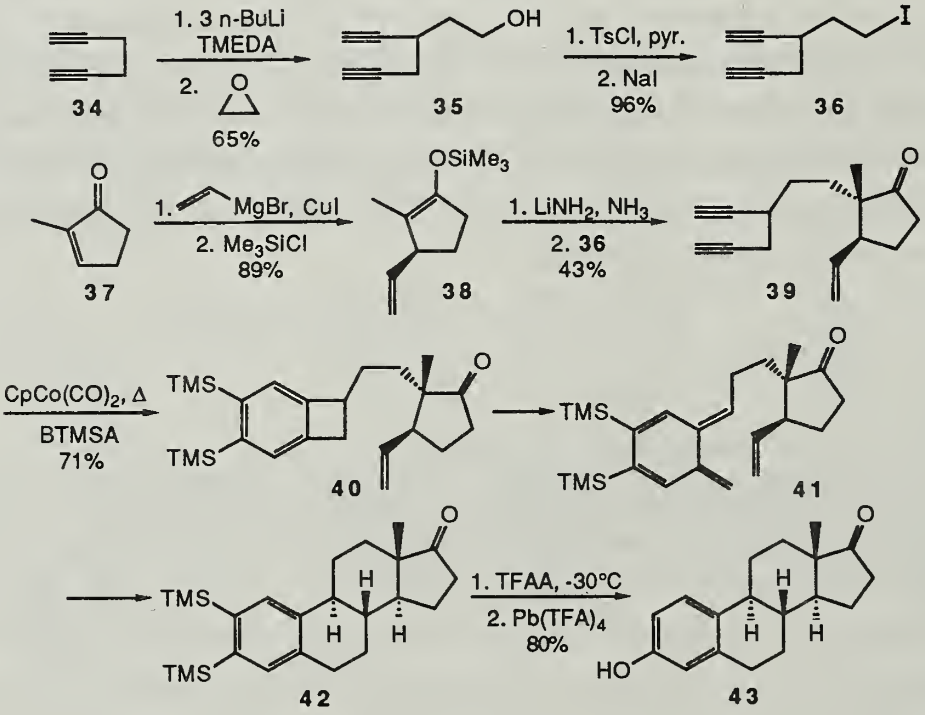
(10)

NATURAL PRODUCT APPLICATIONS

Vollhardt has illustrated the extremely diverse nature of this reaction by the synthesis of a variety of natural products. Although the benzene ring is an important functionality in a number of naturally occurring molecules, retrosynthetic analysis to provide these funtionalities via transition metal mediated cyclotrimerization of alkynes had received no attention prior to Vollhardt's work. In some examples of the scope of cobalt catalysis, Vollhardt described the formation of a number of complex ring systems.[3,25,26]

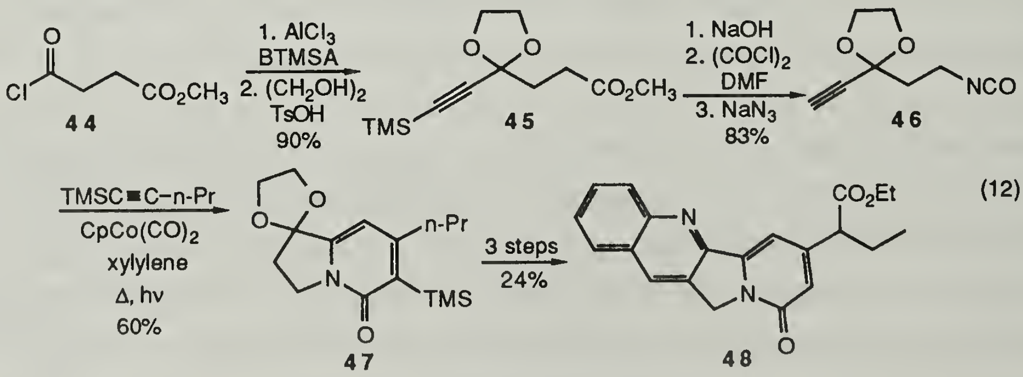
The synthesis of dl-estrone is illustrative. As described earlier, benzocyclobutenes can be readily synthesized via cobalt catalysis of 1,5-diynes with alkynes. These species can then thermally undergo electrocyclic ring opening to give reactive o-quinodimethanes.[27] Vollhardt used this in his synthesis of dl-estrone shown in equation 11.[26a] The first key step involved the diastereoselective synthesis of cyclopentanone **39** by addition of the enolate generated from enol ether **38** to iododiyne **36**. Cobalt catalyzed cooligimerization of BTMSA with diyne **39** gave estratrienone **42** in 71% yield. This one step procedure to produce three new rings in a chemo, regio, and stereoselective manner proceeds through intermediates **40** and **41**. Regioselective protodesilylation followed by lead tetrakistrifluoroacetate oxidation yields dl-estrone **43** in 22%

overall yield from 2-methylcyclopenten-1-one **37** and 15% from 1,5-hexadiyne **34**. Previous syntheses of the steroid ring system were usually lower yielding and required more steps.[27]



(11)

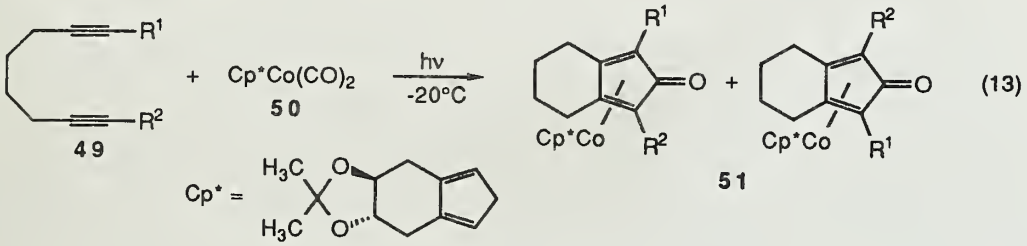
Vollhardt also illustrated the potential of isocyanates in cobalt mediated cocyclizations with alkynes by describing the formal synthesis of the antitumor agent camptothecin as shown in equation 12.[26] The key step in the synthesis involved the regioselective cocyclization of alkyne **46** with 1-trimethylsilylhexyne to give indolizinone **47**. Three additional steps to yield tetracyclic ethyl ester **48** thus completed a formal synthesis of camptothecin (9 steps in 9% overall yield). This synthesis was superior to most of the previous syntheses via intermediate **48** in both yield and number of steps.[28]



(12)

CHIRAL CYCLOPENTADIENYL LIGANDS

Vollhardt has recently explored the potential asymmetric induction of chiral cyclopentadienyl cobalt complexes in the reaction of diynes with carbon monoxide as shown in equation 13.[29] The reaction of diynes **49** with chiral cobalt complex **50** produced a mixture of diastereomers **51** ranging from zero (R^1=$SiMe_3$, R^2=Et) to 34% e.e. (R^1=$SiMe_3$, R^2=Me) in ~65% yield. These are only preliminary results indicating the potential of asymmetric induction in these cobalt mediated cyclizations.



SUMMARY

The use of transition metals for the formal [2+2+2] cycloaddition of alkynes in highly chemo, regio, and stereoselective ways have added another retrosynthetic disconnection not previously considered possible by most synthetic organic chemists. Vollhardt has illustrated the synthetic utility of this process with many examples of one pot multiple ring forming reactions. The synthesis of benzocyclobutenes has been applied to the synthesis of natural products and other molecules of theoretical interest. The introduction of alkenes and other unsaturated functionalities into the catalytic cycle with high stereoselectivity by the use of chiral ligands will undoubtedly play an important role in future synthetic applications.

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ORGANIC SEMINAR ABSTRACTS

1988-89, SEMESTER II

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Semester II, 1988-89

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NONBONDING INTERACTIONS IN BIOORGANIC MOLECULES

Reported by Jon Erickson February 2, 1989

INTRODUCTION

The importance of nonbonding interactions is just beginning to come to the forefront of organic and biochemistry. In biochemistry, these forces have been considered important especially in the area of protein and nucleic acid structure as well as in drug binding. Organic chemists have also seen the value of studying nonbonding interactions to better understand such things as conformational or solvent effects.

What types of forces are involved? The interactions can be classified into two broad categories, enthalpic and entropic. Enthalpic interactions involve mostly long range coulombic energies but orbital overlap (short range) may also play a part at short or intermediate distances. The coulombic energies can be divided into three types. The first arises from dipole-dipole attractions caused by the electrostatic forces between two polar molecules, between a polar and a charged molecule or between charged species. The second is a dipole-induced dipole or induction energy involving a polar or charged molecule and a nonpolar one. The first molecule polarizes the second creating an "induced dipole" from which the coulombic attraction arises. The third type of energy is from an induced dipole-induced dipole interaction also known as dispersion. These attractions are caused by momentary fluctuations in the electronic distributions of two nonpolar molecules which can lead to "instantaneous dipoles" creating a coulombic type of interaction between the two molecules.

The second classification of nonbonding interactions, entropic, involves mainly what is known as the hydrophobic effect. This involves, for example, the forces holding hydrocarbons together in water and arises from an increase in the free energy caused by an increase in the order of the aqueous solvent.

In this account, the general theory behind the enthalpic type of nonbonding interaction will be examined along with a representative review of theoretical attempts to come to a better understanding of this subject.

COULOMBIC INTERACTIONS

Definitions

The basic theory of nonbonding interactions has been recently and very extensively

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reviewed.[1,2] The general equation representing the electrostatic forces is derived from Coulomb's law (equation 1). The interaction energy (E) is proportional to the charges (e) of the

$$E_{electrostatic} = - q_1q_2/4\pi\varepsilon_0 r \qquad (1)$$

two species, 1 and 2, and it falls off as the distance (r) between 1 and 2 increases, where ε_0 is the vacuum permativity and C is a constant. When 1 and 2 are dipoles, the interaction energy is represented by equation 2. Instead of charges, the dipole moments (μ) of the two species

$$E_{electrostatic} = - \mu_1\mu_2/(4\pi\varepsilon_0)r^3 \qquad (2)$$

become important and the interaction energy falls off as r^{-3}. The contributions from higher moments, quadrupole, octapole etc., fall off even faster with increasing distance.

When a nonpolar molecule is placed in an electric field, a second type of coulombic force arises which is known as induction or a dipole-induced dipole interaction. This can occur when the nonpolar molecule comes into contact with a charged or dipolar species. The polarizability (α) of the nonpolar molecule and the charge or dipole moment of the polar molecule are the important quantities in these attractions. The expression for the interaction of a nonpolar molecule and a polar molecule is given in equation 3. The energy is proportional to the dipole

$$E_{induction} = -2\mu_1{}^2\alpha_2/(4\pi\varepsilon_0)^2r^6 \qquad (3)$$

moment or charge of species 1 and the polarizability of the nonpolar molecule, 2. The induction energy falls off with distance faster than the electrostatic case.

The last type of coulombic interaction is between two nonpolar molecules and can be thought of as the interaction between "instantaneous dipoles" which are created by the fluctuation of the electronic distributions of the two molecules. This type of force cannot be derived from classical physics but an approximate representation is given in equation 4. This equation, where

$$E_{dispersion} = -3\alpha^2E_I/4(4\pi\varepsilon_0)^2r^6 = C_6/r^6 \qquad (4)$$

E_I is the ionization energy, represents only the dipolar contribution to the dispersion force. There are also quadrupolar and higher order terms involved in the dispersion interaction (equation 5). The dependence of the dispersion energy on the distance between the two interacting molecules

$$E_{dispersion} = C_6/r^6 + C_8/r^8 + C_{10}/r^{10} \qquad (5)$$

of these higher order terms falls off even faster than the dipolar term.

Methods of Determining Nonbonding Interactions

***ab initio* Calculations.** One way these interactions can be treated is using quantum mechanical methods, particularly perturbation theory.[2] The Hamiltonian operator of the two interacting species is represented by equation 6. It is made up of the unperturbed Hamiltonians,

$$\mathbf{H} = \mathbf{H}_1 + \mathbf{H}_2 + \mathbf{H}' \tag{6}$$

$\mathbf{H}_1$ and $\mathbf{H}_2$, of the molecules, 1 and 2, plus the interaction Hamiltonian, $\mathbf{H}'$, which is treated as a perturbation to the two noninteracting Hamiltonians. The interaction operator is shown in equation 7. The first order term of the perturbation leads to the electrostatic energies while the

$$\mathbf{H}' = (4\pi\varepsilon_0)^{-1} \sum q_i^{(1)} q_j^{(2)} (r_{ij})^{-1} \tag{7}$$

second order term gives rise to the induction and dispersion interaction energies. Problems do arise, however, when using this method. Accuracy is lost without the inclusion of enough terms and this method assumes that there are no orbital interactions so the method is valid only at long range.

Another *ab initio* approach to nonbonding interactions is the variational method. This method involves calculating the potential over the system as a whole, that is, over both of the interacting species. This is a more accurate description of the total potential, but it is difficult to extract the contributions to the overall energy of the particular nonbonding interactions.

A problem with both the variational and the perturbational method is their high computational expense. Because of this, only the interaction potentials between atoms or very small molecules can be calculated and only systems in free space are considered since solvent interactions must be omitted.

Empirical Calculations. Since *ab initio* calculations are far too expensive computationally to calculate nonbonding energies on medium to large molecules, other methods must be developed to approximate the nonbonding interactions in molecules that are of interest to organic and biochemists. The most widely used technique is called the "site-site" method and it has many variations.[1] One of the problems in calculating energies of interacting molecules is there are several distances and orientations to be considered. One way to get around this anisotropy problem is to assume that the interactions between the individual atoms or some other sites in the molecule with atoms or sites in the interacting molecule are additive. Once this assumption is made atom-atom or site-site energies can be calculated over all atoms or sites and the total interaction energy can be found by summing all these energies. This is an empirical method since the parameters of these site-site potentials are often determined from empirical results or from semi-empirical calculations. The contributions to the nonbonding interactions are split up into their constituent parts as shown in equation 8. Here the electrostatic, induction,

$$E_{total} = E_{electrostatic} + E_{induction} + E_{dispersion} + E_{overlap} \tag{8}$$

dispersion and overlap terms are summed over all the sites of both interacting molecules. There are many examples of these site-site methods in the literature and they have been applied to a wide variety of systems.[3]

A typical method was derived by Scott and Scheraga.[4] They used a modified "6-exp" potential along with an exchange term to take into account interaction with adjacent bonds. The potential function is displayed in equation 9, where the first term is to take into account the

$$U(\omega) = 1/2U_0(1 + \cos 3\omega) + \sum \{a_k e^{-b_k r_k} - [c_k/r_k^6] + d_k/r_k\} \tag{9}$$

exchange interactions and the second term is to account for nonbonded interactions and in particular, dispersion. The parameters a_k, b_k, c_k, and d_k were fitted to intermolecular potentials of the noble gases which were derived from molecular beam experiments. Scott and Scheraga also used a Lennard-Jones type potential for studying polypeptide conformations which included terms to account for electrostatic interactions and hydrogen bonding.[5] Scheraga later introduced a more rigorous empirical method in which electrons were treated in addition to nuclei, both as point charges, to obtain the nonbonding potential.[6] Parameters were obtained from experimental values of small molecules which were used as molecular fragments to build the larger molecules of interest. Other methods involved semi-empirical calculations of atomic partial charges to derive the electrostatic term.[7,8] Less rigorous methods were also developed to study the conformations of proteins which treated each amino acid as a hard sphere[9,10] or by setting other geometric constraints[11,12] on the protein to limit the number of conformations.

Other researchers have developed site-site calculation methods to study nonbonded interactions in bioorganic molecules. Brant and Flory used a method to calculate conformations of peptides which included a term for nonbonded interactions.[13] Huron and Claverie[14] included induction (or polarization) terms and also used a monopole approximation[15] instead of the commonly used dipole-dipole term to account for electrostatic interactions. A method was also developed for treating the electrostatic contribution as charge distributions derived from *ab initio* multipole moments[16,17] of small fragment molecules which could be added together to obtain intermolecular[18] and intramolecular[19] nonbonded energies of larger molecules. Other variations were employed such as including interactions with solvent and other molecules in the potential calculation.[20] In addition to the methods mentioned earlier, several studies of the nonbonding interactions in bioorganic molecules have been carried using molecular mechanics programs. Karplus,[21] Kollman,[22,23] Levitt,[24,25] Lifson,[26] and Allinger,[27] for example, have developed molecular mechanical programs which include methods to study nonbonded interactions. Finally, site-site methods have also been developed to study the intermolecular nonbonded energies in crystals to obtain lattice energies.[28,29] The potentials used are similar to those mentioned earlier in that the parameters are fitted to experimental data but, in this case, sublimation energies and x-ray crystallographic data are available.[28]

An alternative method for calculating nonbonded intermolecular interactions is to use the convex-core potential method.[30] This technique differs from the site-site method in that instead of a sum of site-site terms, a single term is used (equation 10). A hard convex core is chosen

$$U(\rho) = U_0[(\rho_0/\rho)^{12} - 2(\rho_0/\rho)^6] \tag{10}$$

inside the molecule which is appropriate to the shape of the molecule. When two of these molecules interact the potential shown in equation 10 is used where ρ is the distance between the two cores. The main advantage to this method is molecular shapes can be better accounted for than in the site-site method, but it is not nearly as accurate when applied to large polyatomic molecules.[1] It is very useful, however, in obtaining such properties as second virial coefficients.[1,3,30]

HYDROGEN BOND INTERACTIONS

Definition

Of all the nonbonding interactions in bioorganic molecules, the hydrogen bond is one of the most important. This is largely due to its wide occurrence in proteins, making up their secondary and tertiary structure, and also in the helical structures of DNA. Hydrogen bonds are usually grouped into two categories, strong and weak.[1,31] Strong hydrogen bonds occur between a charged species and a hydrogen atom bonded to an electronegative atom such as nitrogen and oxygen. Weak hydrogen bonds occur between a hydrogen atom bonded to an electronegative atom and another electronegative atom either in the same molecule or in a different molecule. The latter type is the most important in bioorganic systems. Since hydrogen bonds are nonbonded interactions between a hydrogen and an electronegative atom, they are made up of the same types of nonbonding interactions described earlier as shown in equation 11 with the

$$E_{\text{H-bond}} = E_{\text{electrostatic}} + E_{\text{induction}} + E_{\text{dispersion}} + E_{\text{overlap}} + E_{\text{charge-transfer}} \qquad (11)$$

addition of a charge-transfer term which is thought to be important in hydrogen bonding.[31]

Methods of Determining Hydrogen Bonding Interactions

***ab initio* Calculations.** As in the case of the generalized nonbonded interactions, both perturbative and variational methods have been used, but only for hydrogen bonds between small systems such as $(H_2O)_2$ and $(HF)_2$ where solvent contributions are omitted.[31] These calculations do, however, give information on some general properties of the hydrogen bond which are in fair agreement with experiment, for example, equilibrium geometries, bond force constants, electric multipole moments, polarizabilities and chemical shifts.[31] The bond angle, X—H---Y, is ideally close to 180° and is very important to the strength of weak hydrogen bonds. Infrared absorption intensities increase upon hydrogen bonding and a downfield shift in the nmr spectrum of the hydrogen bonded hydrogen is observed. The charge transfer contribution has been calculated by an integrated density difference function, the difference in the electron density between the two isolated molecules and the whole system, from atom charges derived from a population analysis or from partitioning SCF wavefunctions at large distances.[31] Problems may arise, however, even using high levels of theory upon small molecules. One of these is due to basis set truncation and procedures have been used to correct them.[32,33] It appears that the contributions of the nonbonding terms to the weak hydrogen bond are in the order $E_{\text{electrostatic}} > E_{\text{overlap}} > E_{\text{dispersion}} \approx E_{\text{induction}} \approx E_{\text{charge-transfer}}$ where the electrostatic term represents roughly 80% of the energy of the hydrogen bond.[1,31]

Empirical Calculations. Even though *ab initio* calculations of small molecules provide good information about the general properties of hydrogen bonds, to study these interactions in large bioorganic molecules, empirical methods must be employed. Many of the techniques described earlier to calculate nonbonding interactions include terms that compensate for hydrogen bond formation. An example is the explicit term that Scott and Scheraga used in their potential to study the conformations of peptides.[5] They included contributions from bond and hydrogen bond stretching, dispersion and electrostatics in their hydrogen bonding term. They later used a Lennard-Jones type of potential which consisted of a "10-12" rather than the usual "6-12" potential and was parameterized with x-ray crystallographic data.[7,8] This same type of "10-12" Lennard-Jones potential function was also used by Kollman in accounting for hydrogen bonding.[22] Others have used a "6-12" potential but added an angular dependance to the function.[34] Karplus and co-workers used a "switching function" that, depending on the hydrogen bond angle and length, would include an explicit, distance and angular dependent, function to account for hydrogen bonds.[21] In the absence of a potential function, an approximate equation was developed that treated the hydrogen bond as the simple interaction between a polar bond and a lone pair of electrons.[1,31]

Since hydrogen bonds are important in crystals of organic and bioorganic compounds methods for calculating nonbonding interactions in crystals include hydrogen bond terms. For example, Kitaigorodsky[28] used a term similar to Sheraga's[5] and Claillet and Claverie[29] used a switching function in which the overlap term is reduced at the short distances which occur in hydrogen bonds.

Charge transfer is thought to be important in hydrogen bonding, but the contribution to the hydrogen bond from charge-transfer is difficult to extract from the overall energy. *Ab initio* methods, described earlier, have been devised to isolate the charge transfer contribution, but few empirical schemes are known. Recently a method has been formulated,[35,36] where the charge-transfer term is extracted from the dispersion term using an approximation derived from perturbation theory.

SHORT RANGE INTERACTIONS

Definition

When two molecules approach within van der Waals contact of each other, their electronic distributions begin to mingle. This causes a strong repulsive force when both of the molecules have filled valencies, due to the Pauli exclusion principle, and is commonly known as steric repulsion. The alternative is if one of the interacting orbitals is not full then a short range interaction may result in a covalent bond. This behavior can be illustrated by the familiar Lennard-Jones "6-12" potential in which the dependence on distance switches from a $-r^{-6}$ at large distances to a $+r^{-12}$ at short range.

Methods of Determining Short Range Interactions

***ab initio* Calculations.** *Ab initio* calculations are very important when determining the effects of short range forces due to the quantum mechanical nature of the interaction. One problem is the indistinguishability of the electrons. When molecules begin to interact, the calculated orbitals of both molecules mix causing their electrons to become artificially indistinguishable from each other.[2] A method to overcome this difficulty uses a wavefunction which is antisymmetric to both molecules.[2] Another way is to calculate the energy of each molecule individually and together and then find the difference.[2] Again, due to the number of orientations to consider and the computational expense of *ab initio* calculations, they have not been employed except in the case of atoms and very small molecules.

Empirical Calculations. An approximate expression has been developed stemming from the Hellman-Feynman theorem which treats the repulsive interaction at short distances as an overlap force rather than an exchange force, which would require a quantum mechanical treatment.[1] The expression is given in equation 12 and has lead to quite accurate

$$U_{overlap} = Ae^{-Br} \tag{12}$$

results. Applications to bioorganic molecules have used many terms to take into account the short range repulsion. Scheraga and co-workers used a form similar to equation 12 for orbital overlap.[6] Others have considered interactions between bonds and between bonds and lone pairs, treating the lone pairs as pseudo atoms.[18,19] The potential involved a combination of dispersion and repulsion terms where the repulsion term was made up of the product of an exponential and a constant similar to that in equation 12.[14] This type of term was also used in the case of crystals.[28,29] In studies involving peptide conformation, rotation barriers were considered in the repulsive term which was made up of a constant energy barrier with a rotation angle dependance (see the first term in equation 1).[4,5,7] Molecular mechanical programs have included terms for deformations of bond lengths, angles and dihedral angles assuming these changes to be harmonic and an improper torsional term for anharmonic vibrations.[20,21,22,23]

CONCLUSION

In this report, an attempt has been made to shed some light on the problems involved in calculating accurate magnitudes of nonbonding interactions in bioorganic systems. Many attempts have fallen short of this goal due to the inadequacy of empirical approximations which must be made in order to make computation of large molecular systems feasible. The non-additivity problem of long range interactions along with the inability to calculate accurately forces at short and intermediate distances must be addressed before quantitative solutions can be found. Nevertheless, very useful information can be obtained from site-site methods if they are used in light of the approximations made and in conjunction with experimental results.

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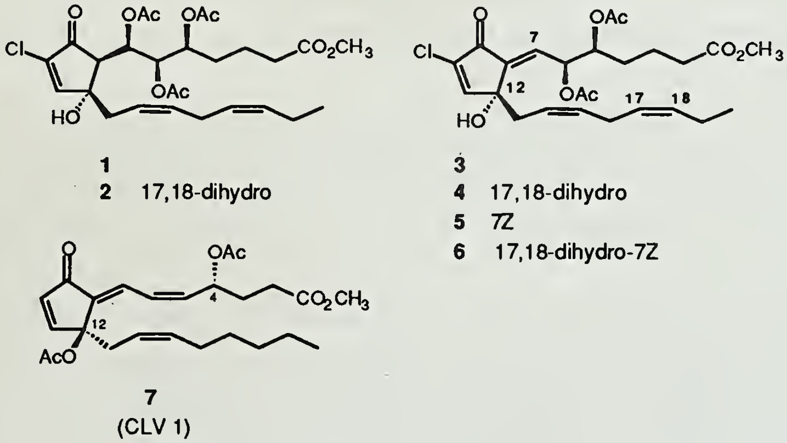
SYNTHESES OF PUNAGLANDINS

Reported by Brenda S. Kesler February 6, 1989

INTRODUCTION

Although prostaglandins have been thoroughly studied by chemists, there continue to be discoveries of structural analogs that show even more promise as therapeutic drugs. Two structurally related marine eicosanoids, the punaglandins (**1-6**)[1] and the clavulones (**7**)[2] show even greater anticancer and antiinflammatory properties than the prostaglandins.[3] The clavulones were the first prostanoids to show C-4 and C-12 oxygenation. This led Corey[4] to propose that their biosynthetic pathway is distinct from that of the prostaglandins. The punaglandins (PUG) also have C-12 oxygen substitution and have additional unprecendented C-10 chlorine substitution. The presence of these unique groups is presumably responsible for enhanced biological activity of the clavulones and punaglandins.



1
2 17,18-dihydro

3
4 17,18-dihydro
5 7Z
6 17,18-dihydro-7Z

7
(CLV 1)

Figure 1

Six punaglandins were isolated from the Hawaiian octocoral *telesto riisei* by Scheuer[2] in 1985 (Figure 1, **1-6**). Their structures and absolute stereochemistry were assigned at this time, albeit incorrectly. Of these, PUG **4** shows the highest biological activity, and for this reason its syntheses and that of its 7Z isomer (**6**) will be discussed here. Both Yamada[5] and Noyori[6] published syntheses of PUG's **4** and **6** in 1986. Their work led to the correction of the absolute stereochemistry at C-12 to that shown in Figure 1. The only other synthesis of PUG **4** to date, that of Shibasaki,[7] will also be discussed.

SHIBASAKI'S SYNTHESIS

Retrosynthetic analysis

The strategy for all three syntheses of PUG **4** rely on the same initial disconnection, removal of the α-side chain to give a chlorinated cyclopentenone and the corresponding

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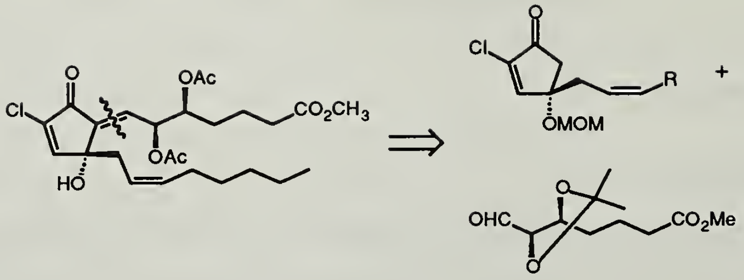
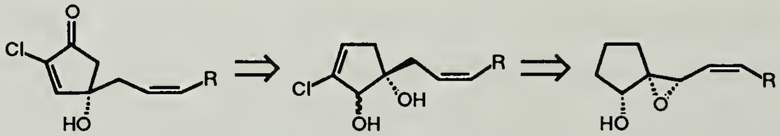
Scheme I



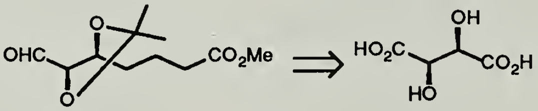
aldehyde as shown in Scheme I. Shibasaki realized that the cyclopentenone moiety could arise via an allylic displacement. The diol precursor might be prepared by asymmetric epoxidation as

Scheme II



shown in Scheme II. The aldehyde subunit could be synthesized from tartaric acid, if appropriate differentiation between the two identical ends could be achieved (Scheme III).

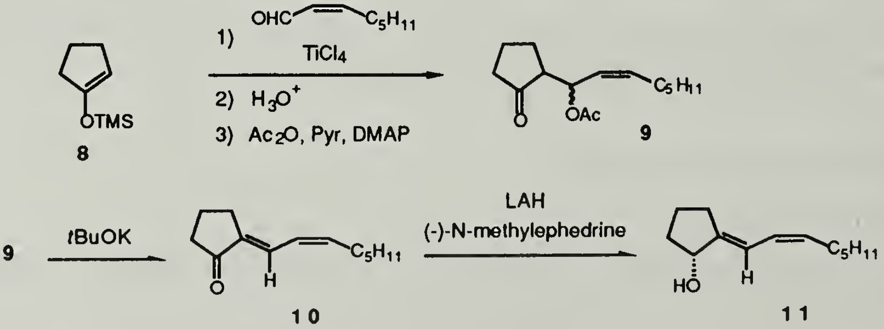
Scheme III



Synthesis

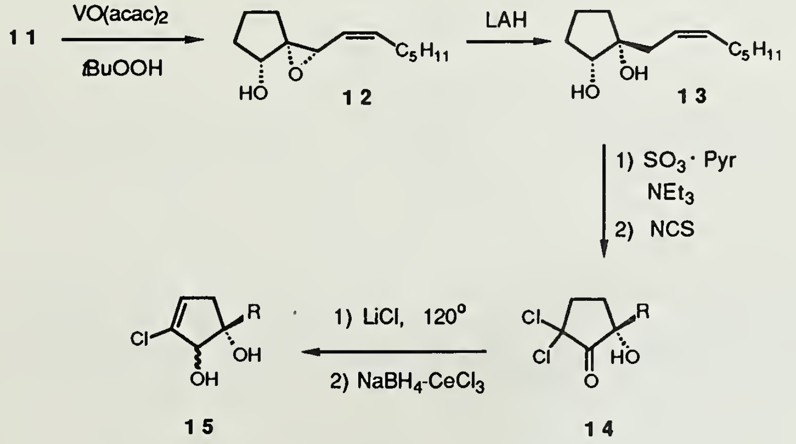
Shibasaki's synthesis of the cyclopentenone portion of PUG **4** began with 1-[(trimethylsilyl)oxy] cyclopentene (**8**). Treatment of **8** with (Z)-2-octenal under Lewis acid conditions, followed by an aqueous acid workup and protection of the initial acetate gave **9**. Reaction of the acetate with potassium *tert*-butoxide formed the dienone **10** by elimination as the only product. The key step to the synthesis of the cyclopentenone portion was efficient asymmetric reduction of this dienone. After a brief survey, a 91% yield and 96% ee of the required alcohol (**11**) was obtained by means of lithium aluminum hydride (LAH) that was modified by use of (-)-N-methylephedrine[8] and 2-(ethylamino)pyridine (Scheme IV).

Scheme IV

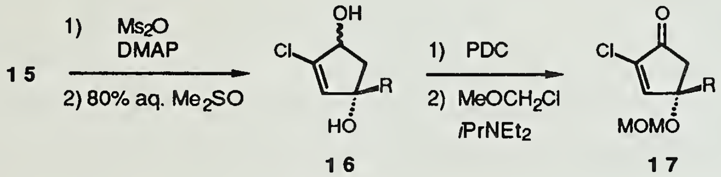


Compound **11** was epoxidized stereospecifically with *tert*-butylhydroperoxide and vanadyl-acetylacetonate.[9] This set the absolute stereochemistry at C-12. Epoxide (**12**) was treated without isolation with LAH to afford diol **13**. Oxidation and chlorination of **13** gave **14**. Its dehydrochlorination and reduction produced diol **15** (Scheme V) which was the key precursor for Shibasaki's allylic displacement reaction. The key step in Shibasaki's synthesis of punaglandins **4** and **6** is a 1,3 oxygen transfer. This was accomplished by selective mesylation of secondary alcohol **15**, followed by solvolysis to give the rearranged diol **16**. Note also that the stereochemistry of the nucleophilic attack and at the leaving group is unimportant. Oxidation with PDC followed by protection completes the synthesis of the cyclopentenone portion of PUG **4** (Scheme VI).

Scheme V

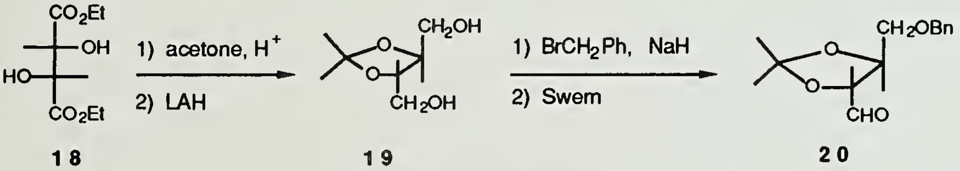


Scheme VI



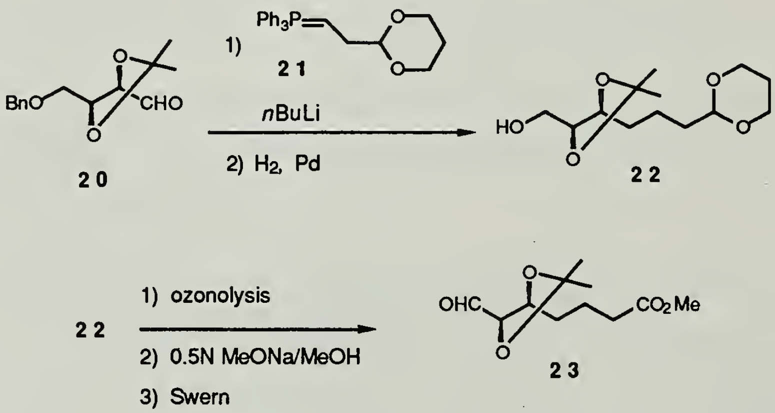
The synthesis of the aldehyde that was used to form the α-side chain of PUG **4** began with the ethyl ester of L-(+)-tartaric acid (**18**). According to the method of Feit,[10] formation of the acetonide followed by reduction of the esters with LAH produced 2,3-O-isopropylidene-L-threitol (**19**). Application of Seebach's procedure[11] for monobenzylation of **19**, followed by Swern oxidation of the product gave 4-O-benzyl-2,3-O-isopropylidene-L-threose **20** (Scheme VII). This substance was converted to **22** by the Wittig reaction of **20** with the phosphorane

Scheme VII

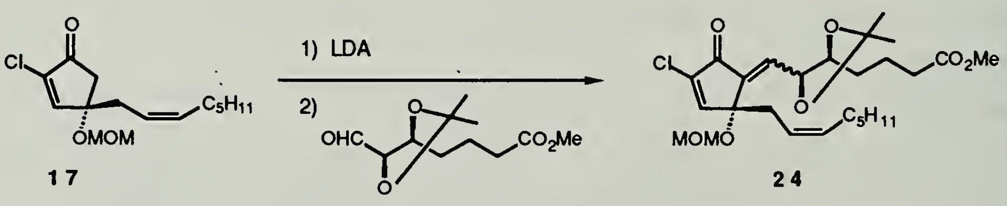


21[12] followed by catalytic hydrogenolysis. Ozonolysis of the acetal[13] and transesterification gave the hydroxy ester which was converted to aldehyde **23** by a Swern oxidation as shown in Scheme VIII. Aldehyde **23** was coupled to **17** to give protected punaglandin **24** (Scheme IX). Selective hydrolysis of the acetonide followed by acetylation and deprotection of the tertiary alcohol afforded PUG's **4** and **6** in a 1% overall yield for 20 steps.

Scheme VIII



Scheme IX

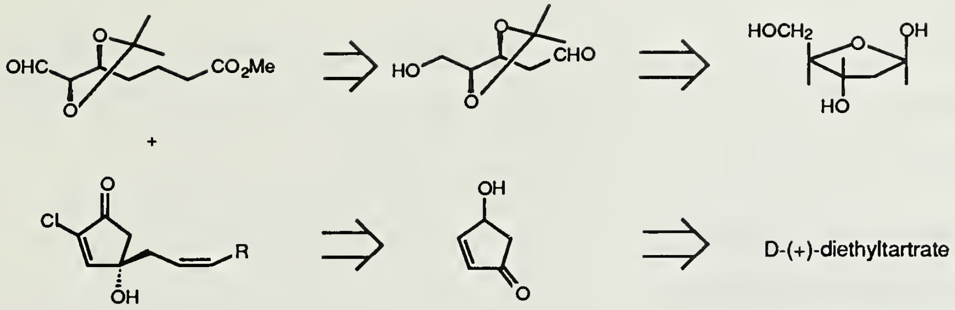


YAMADA'S SYNTHESIS

Retrosynthetic analysis

Like Shibasaki, Yamada used tartaric acid as one of the starting materials for the synthesis of PUG **4**. However in this case tartaric acid was used to direct the nucleophilic attack of the *t*-butylacetate anion, thus establishing the stereochemistry at C-12 of the cyclopentenone portion of PUG **4**. In this synthesis, the α-side chain of PUG **4** might be obtained from 2-deoxy-D-ribose using routine transformations. Both stereocenters would be obtained from the sugar itself (Scheme X).

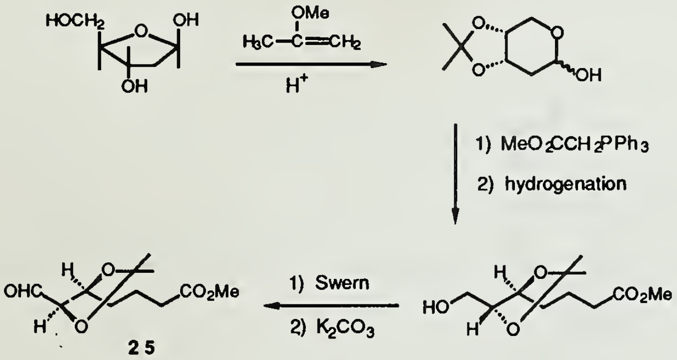
Scheme X



Synthesis

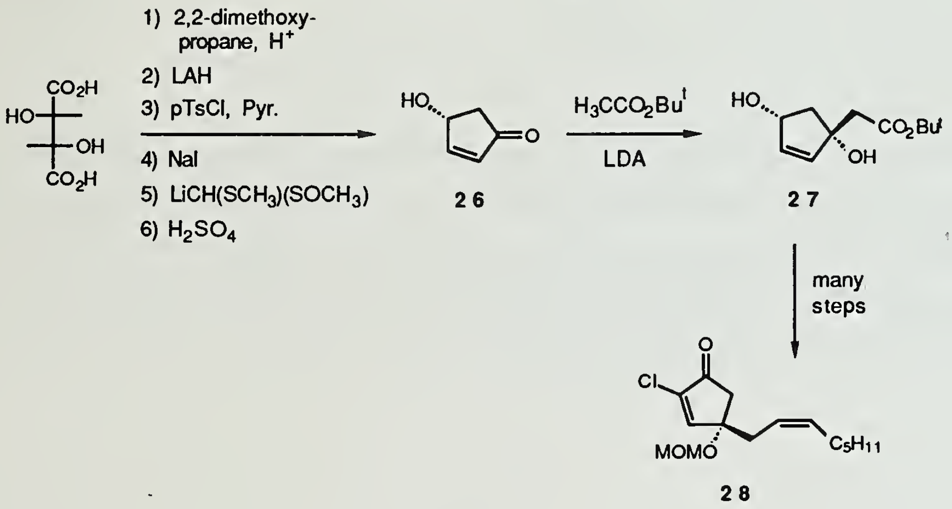
The α-side chain was constructed using the routine series of transformations shown in Scheme XI. The stereocenters required in the product are already present in the starting sugar.

Scheme XI



Following the procedure of Ogura,[14] synthesis of the cyclopentenone portion of PUG **4** began with D-(-)-tartaric acid to produce (R)-4-hydroxy-2-cyclopentenone (**26**). The C-9 alcohol directed the nucleophilic addition of *t*-butylacetate to produce **27.** This established the stereochemistry at C-12. A series of oxidations, protections and additions led to compound **28**

Scheme XII



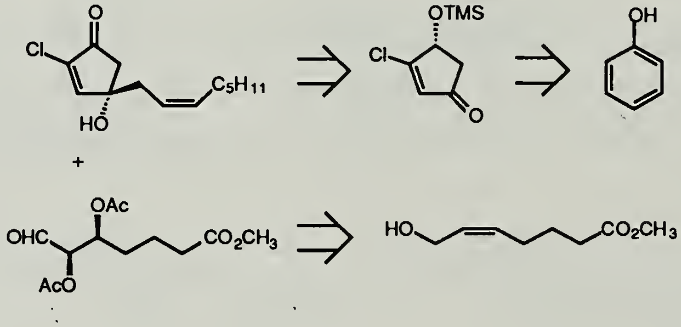
(Scheme XII). As shown previously, coupling of **28** with aldehyde **25**, followed by dehydration and protecting group manipulations produced punaglandin **4** and **6** in a 1.6% overall yield for 21 steps.

NOYORI'S SYNTHESIS

Retrosynthetic analysis

Noyori's synthesis differs in that no use is made of the "chiral pool" of reagents. Removal of the ω-side chain left the cyclopentenone shown which might be produced from a ring contraction of phenol[15]. The stereochemistry of the α-side chain was controlled by means of Sharpless asymmetric epoxidation. (Scheme XIII).

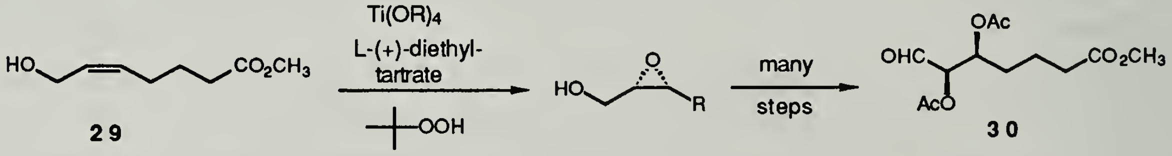
Scheme XIII



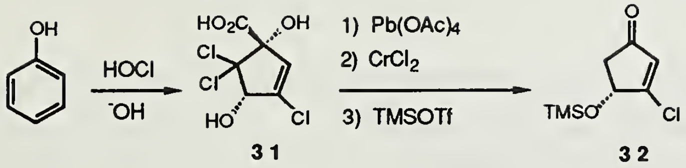
Synthesis

Z-allylic alcohol (**29**) was converted to **30** by the Sharpless asymmetric epoxidation[16] followed by routine chemical reactions (Scheme XIV). Synthesis of the cyclopentenone portion of PUG 4 began with phenol. A ring contraction of phenol using alkaline hypochlorite produced **31** as a racemic mixture. Resolution by formation of the diastereomeric brucine salts gave the 1R, 3S-enantiomer **31** after hydrolysis. Oxidative decarboxylation with lead tetraacetate followed by partial dechlorination and protection of the alcohol as the silyl ether produced **32** as shown in Scheme XV.

Scheme XIV

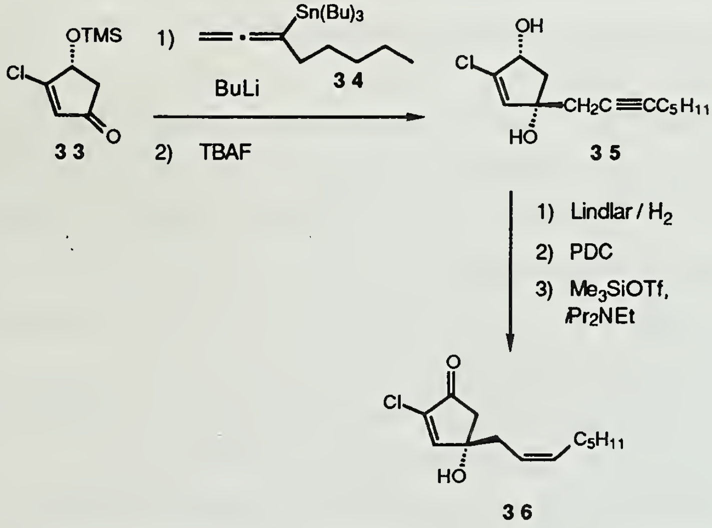


Scheme XV



Introduction of the ω-side chain was accomplished using Noyori's allenyl tin reagent (34).[17] Addition of the allenyl tin to 33 followed by deprotection with tetrabutylammonium fluoride gave 35. Hydrogenation of the resulting alkyne using Lindlar's catalyst followed by oxidation and protection gave 36. Coupling of 36 and 30 afforded PUG 4 and 6 in a 1% overall yield in 14 steps (Scheme XVI).

Scheme XVI



CONCLUSION

In summary, the synthesis of punaglandins 4 and 6 has been achieved in three separate groups. Shibasaki's synthesis focussed on an efficient asymmetric reduction for a dienone as well as an allylic rearrangement to set up the correct oxygen substitution. The approach taken by Yamada was also to use chiral starting materials to obtain the correct stereocenters in the product. Noyori on the other hand used well precedented chemistry *e.g.* the Sharpless asymmetric epoxidation, as well as his novel allenyl tin chemistry, to introduce the necessary chirality and thus achieve the total synthesis of punaglandins 4 and 6.

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DESIGN AND MODE OF ACTION OF INTERCALATIVE BLEOMYCIN AMPLIFIERS

Reported by Tom Perun

February 9, 1989

INTRODUCTION

The bleomycins (BLM) are a group of glycopeptide antitumor antibiotics isolated from the fermentation broth of *Streptomyces verticillus* .[1] BLM causes both single-strand and double-strand breaks in DNA[2] both in vivo[2b-d,3] and in vitro.[2b,4] Strand breakage was believed to cause inhibition of cell growth[5] and cell death,[6] although the results are not conclusive and recent results show there is no direct correlation between breakage and cell death.[7]

Because of BLM's toxicity it can be used clinically only in small amounts, and requires other antitumor agents to provide useful results.[8] Alternatively the potency of BLM may be increased by agents which are not themselves active. These compounds, called amplifiers, increase the effectiveness of BLM by increasing cellular uptake of BLM,[9] or reducing regeneration of cleaved DNA,[10] or increasing DNA cleavage.[11]

Amplifiers of BLM's antitumor activity which increase cleavage, through intercalating with DNA, have been developed by elaboration of classical fused ring intercalators[11a,b,d] and now include unfused bicyclic and tricyclic polyaromatic intercalators.[11e] The synthesis of unfused amplifiers has provided the opportunity to study the structural features required for intercalation and the effect of intercalation on amplification.[12]

CLASSICAL INTERCALATORS

Ethidium bromide (EB) has been extensively investigated as a possible amplifier of BLM's antitumor activity by increasing cleavage of DNA by BLM.[11a,b,d] Initial studies by Bearden and Haidle[11a] were done on double-stranded DNA incubated in vitro with BLM and varying concentrations of EB. The results show that EB has a concentration dependent synergistic effect on DNA cleavage by BLM. The maximum amount of cleavage occurs at an EB concentration of 2.5×10^{-4} M, while at higher concentrations inhibition is seen. The optimum concentration corresponds to a ratio of 1 EB molecule per DNA nucleotide. At this ratio there are no sites for BLM to intercalate, a necessity for DNA cleavage,[13] and therefore only a portion of the EB must be intercalated. Another explanation is that EB is binding to the outside of the helix.[14] But studies with single stranded DNA indicate that this binding inhibits cleavage by BLM.[11a] However, since the DNA was incubated simultaneously with BLM and EB in these experiments, it is possible that BLM could bind before all the binding sites are occupied by the large amount of EB. At high concentrations of EB, where inhibition of DNA cleavage is seen, a total blockage of

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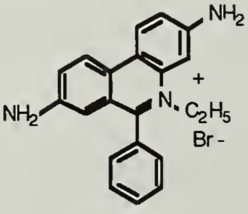
the intercalating sites necessary for BLM to cleave DNA, possibly due to preferential intercalation of EB, is probably inhibiting cleavage.



EB

One explanation for the enhanced efficiency of BLM in the presence of EB is that the intercalation of EB changes the structure of DNA, making it more easily attacked by BLM.[11a,b] A change in structure was first noticed in the micrococcal nuclease degradation of chromatin DNA.[15] In this case it was proposed that EB unwinds the DNA allowing new sites for nuclease degradation. This unwinding may provide new sites for attack by BLM since it cleaves preferentially at the same region of DNA as micrococcal nuclease.

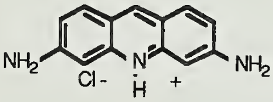
Subsequent studies by Chapman and Nasir,[11d] conducted in a similar manner as Bearden and Haidle,[11a] on EB amplification show that 0.25×10^{-5} M EB decreases the binding of BLM, but increases its cytotoxicity. No results of DNA cleavage were reported. Other experiments show that this concentration of EB increases cleavage of DNA.[11f] These findings indicate that the amount of binding is not directly related to cytotoxicity, and that the intercalation of EB may direct BLM only to intercalation sites where it can cleave DNA. This explanation seems reasonable since cleavage must occur to produce cytotoxicity.[5,6,16]

Chapman and Nasir[11d] also studied the effect of elevated temperature on EB amplification of DNA cleavage by BLM. They observed that increasing the temperature of the BLM DNA reaction from 37 °C to 43 °C increases binding only 14% while cytotoxicity is increased 31%. Other results show BLM binding is still lowered by EB, and the synergistic effect between BLM and EB is gone, although the cytotoxicity is greater than at 37 °C because EB becomes significantly cytotoxic at 43 °C. These results also indicate that cytotoxicity and BLM binding are not directly related, and thus indicate that the hypothesis of BLM direction by EB to specific intercalation sites may be correct. Also, since the synergistic effect is gone at elevated temperature, these treatments don't seem worthwhile.

Experiments by Beerman and co-workers[11b] were done to determine the effect of BLM on DNA preincubated with EB. Results show that optimum amplification occurs when EB is preincubated with DNA in a ratio of EB to DNA of 1:100. Smaller amplification is seen with reversed order or simultaneous incubation of EB and BLM. This ratio is much different than that observed by Bearden and Haidle.[11a] The ratio difference may be the result of preincubating, rather than simultaneously incubating the EB. Since very little EB per DNA is needed when preincubated, it has been suggested that the EB creates sites that are cleaved with increased efficiency.

With the amplification of DNA cleavage realized and optimum experimental conditions determined, work started on the effect of EB amplification on a variety of tumor cells treated in vitro with BLM. Chapman and Nasir[11d] showed that incubation of BLM (20 μg/ml) and EB (5 μg/ml) simultaneously for 60 minutes at 37 °C amplified growth inhibition of human adenocarcinoma cell line, HT29R. Beerman and co-workers[11b] determined the synergistic effect of EB followed by BLM on inhibiting growth of mouse L1210 leukemia cells. First, the concentration that inhibited 50% of cell growth (ID_{50}) was determined for EB and BLM alone. Then when 12% of these concentrations was all that was required for an ID_{50} when EB and BLM were used together, it represents an eight fold synergism. Beerman and co-workers[11c] also determined the effect of EB followed by BLM on human HeLa cervical carcinoma, human HEC-1A endometrical carcinoma, and human V110 colon carcinoma cells lines. Synergistic effects on inhibition of growth is seen for the HEC-1A and HeLa cell lines. The V110 cell line, a tumor quite resistant to single chemotherapeutic agents, disappointingly seems to be unaffected by the combination of BLM and EB.

Other intercalators were also studied as possible amplifiers of BLM and phleomycin, a compound closely related to BLM. The known intercalator, proflavine (PRF), amplifies DNA cleavage, by BLM, about the same as EB.[11a] Many other intercalators, such as the amino acridines, enhance the breakdown of DNA by phleomycin and BLM in *E. coli* B cells.[17] Several bicyclic fused heteroaromatic compounds display antitumor activity in vivo when used with phleomycin.[18] Although the mechanism of action is not described, an intercalation and subsequent DNA unwinding mechanism seems reasonable based on the size of the aromatic ring.



PRF

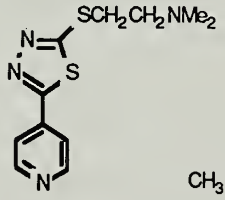
UNFUSED COMPOUNDS

The positive results of using classic intercalators, and their undesirable characteristic of inhibition of cleavage at high concentrations provided the incentive to design and study other possible amplifiers.

Bicyclic

Unfused heterobicyclic compounds were first shown to amplify phleomycin's in vitro antibiotic activity by Brown and Grigg.[18] Later Brown and co-workers[19] showed that another unfused compound (**1**) amplifies BLM-B_2 's activity against Ehrlich's tumor in mice. The T/C ratio, where C is the lifetime of mice treated with BLM B_2 only, and T is the lifetime of mice treated with BLM B_2 plus **1** is about 2.88. These results indicate that unfused compounds may be excellent amplifiers.

A number of compounds (**2-13**) all having an unfused bicyclic structure with varying substituents and rings were synthesized by Strekowski, Wilson and co-workers[12] to study the structural requirements needed for maximum binding. First, they determined which compounds intercalated with DNA using viscometric titration and NMR spectroscopy. ^1H NMR spectroscopy of compounds **2-13** showed that the chemical shifts of the aromatic protons or protons on substituents on the aromatic rings are shifted upfield between 0.44 and 1.07 ppm. It was also observed that the viscosity of DNA, in solution with **2-13**, increased. Both of these observations indicate that **2-13** intercalate, since it is known that intercalators increase the viscosity of DNA,[20a,b] and that intercalation of aromatic groups causes upfield shifts in their ^1H NMR spectra.[20]



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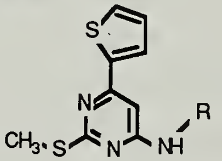

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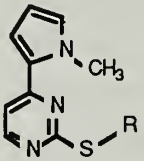

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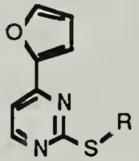

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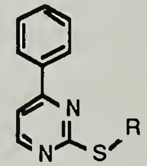
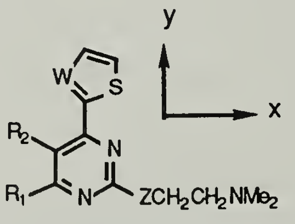


13

$R = CH_2CH_2NMe_2$

cmp	w	z	R_1	R_2
2	CH	S	H	H
3	CH	S	Me	H
4	CH	S	H	Me
5	CH	O	H	H
6	CH	NH	H	H
7	N	S	H	H
8	N	NH	H	H
9	CH	NH	SMe	H



2-9

Strekowski, Wilson, and co-workers[12] then compared similar structures to determine what structural characteristics are important for strong intercalation. Studies on compounds **2-13**, by means of NMR spectroscopy and dipole moment calculations, show that the compounds with the highest binding, **2**, **3**, and **4** determined spectrophotometrically, have positive ends of dipoles x and y, shown in the structure of compounds **2-9**, away from the side chains. This orientation of dipoles results in lower electron density in the aromatic rings resulting in stronger intercalation with electron rich DNA base pairs.

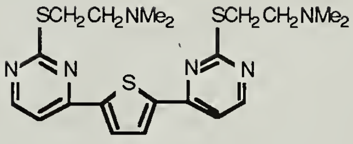
The amplification of BLM's cleavage of DNA was then determined for these unfused compounds. Viscosity measurements were used to determine amplification activity since cleavage of DNA decreases its viscosity.[12] Compound **4** was determined to be the strongest amplifier. Also, all these unfused compounds amplify cleavage of DNA, even at ratios where the classic intercalators are inhibitory. This result indicates that the intercalation of these unfused compounds must be different than the classic intercalators. One explanation is that the dissociation of the unfused amplifiers from DNA is much faster than the fused compounds, and thus allows interaction of BLM. Another explanation is that compounds **2-13** intercalate in the major groove of DNA, and therefore don't interfere with BLM binding, which is believed to occur in the minor groove.[21] This explanation is supported by results that show inhibition of BLM's activity occurs with bithiazole analogs of BLM.[22] The high activity of **4**, relative to other closely related compounds, is probably due to the torsional angle of the two rings which alleviates the steric interaction between the methyl group of the pyrimidine and the proton on carbon w of the pyrrole.[23] This torsional angle results in a twisted structure which can intercalate in a nonclassical manner in which the molecular twist of the hydrogen bonded DNA base pairs is retained,[24] thus forming a stronger interaction which causes more changes in the DNA structure and allows BLM to more effectively cleave DNA.[12]

Tricyclic

Strekowski, Wilson, and co-workers[11e] also synthesized an unfused tricyclic compound (**14**) closely related to the bicyclic compound to determine whether a tricyclic structure can be used as an amplifier. Compound **14** was also shown to intercalate using viscosity measurements and NMR spectroscopy, and shown to have a higher DNA binding constant, and to cause more cleavage of DNA by BLM than compounds **2-13**, possible due to higher conformational freedom. Although **14** has not been tested with BLM in vitro or in vivo against tumor cells, it would be surprising if this compound was not highly effective in these assays.

Polyamine

Strekowski, Wilson, and co-workers[25] also synthesized a bicyclic polyamine (**15**) to study the affect of amino groups on amplification. Compound **15** is protonated in water and amplifies DNA cleavage by BLM two to five times better than the mono amino compound **2**, depending on ratio to DNA. This indicates that the electrostatic interaction between the protonated amine and the negatively charged phosphate backbone of DNA seems to be important for amplification.



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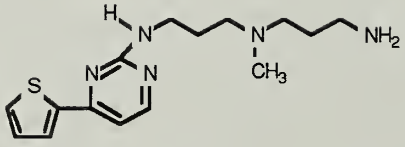

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CONCLUSION

Although the exact mechanism of BLM amplification may not be fully understood, it is clear that DNA intercalators are capable of amplifying BLM's cleavage of DNA, resulting in better in vitro and in vivo treatment of tumor cells. Extensive work by Strekowski, Wilson, and co-workers[11e,23,25] has extended the structural requirements necessary for intercalators to be effective amplifiers. Using these structural necessities, further work should result in better amplifiers which can be used in cancer treatment.

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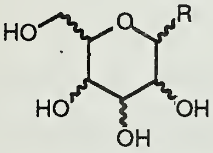
STEREOSELECTIVE SYNTHESIS OF C-GLYCOSIDES FROM CARBOHYDRATES

Reported by Dirk Reif February 20, 1989

INTRODUCTION

The stereoselective synthesis of the polyhydroxylated 2,6-disubstituted tetrahydropyran ring moiety **1**, formally a C-glycoside (Figure 1), has received a great deal of attention over the past ten years. The interest in C-glycosides evolves from their occurrence as subunits in a variety of medicinally important natural products as well as their increased utilization as synthetic intermediates.[1a-c] The monosaccharides are especially attractive for the synthesis of C-glycosides. These sugars have established relative and absolute configurations, which through functional group interconversions, give access to a variety of functionalized tetrahydropyran ring systems. The value of starting with carbohydrates in the stereoselective synthesis of C-glycosides is only realized if stereoselective carbon-carbon bond formation at the anomeric center can be accomplished. Synthetic techniques involving carbocation, carbanion, and radical generation at the anomeric center provide a complementary group of reactions for the stereoselective synthesis of α- and β-C-glycosides.



1 R = alkyl

Figure 1

ELECTROPHILIC ANOMERIC CENTER

Two techniques that rely on the electrophilic character of the anomeric center in carbohydrates have been developed for the stereoselective synthesis of C-glycosides. One method involves the loss of a nucleofuge situated at the anomeric center to give a pyran oxocarbenium ion.[2] The second method proceeds by a direct S_N2 displacement at the anomeric center.[3]

Pyran Oxocarbenium Ions

C-1 activation of a suitably protected glycopyranose followed by reaction with trimethylsilyl nucleophiles under Lewis acidic conditions gives predominantly α-C-glycopyranosides.[4-8] Since either anomer of the starting glycopyranose produce α-C-glycopyranosides, an intermediate pyran oxocarbenium ion has been invoked[4,5] to explain the stereoselectivity observed in these reactions.

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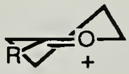
The oxocarbenium ion is believed to adopt a twist chair $^3H_4$ conformation **2** (Figure 2) and the nucleophiles attack from the α (axial) side due to the anomeric effect.[6]

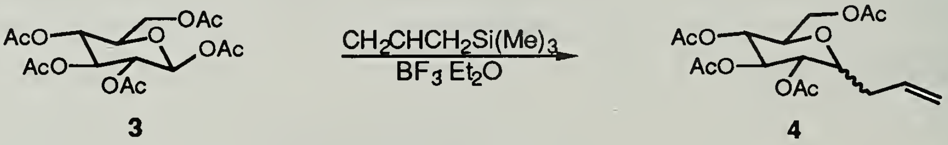


2

Figure 2

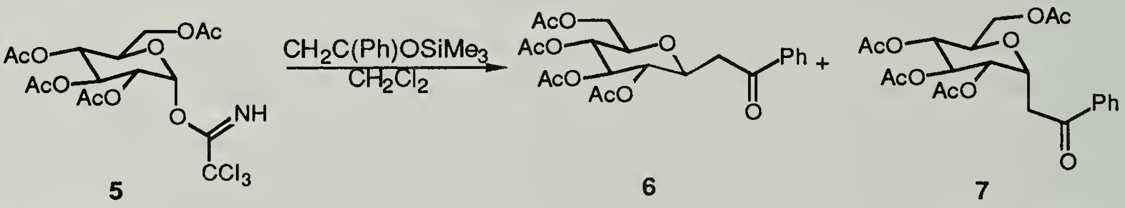
The stereoselectivity in these reactions is dependent on solvent[4], Lewis acid[5], and configuration of the carbohydrate[6] at centers other than C-1. Reaction of 1,2,3,4,6-tetraacetyl-glucopyranose **3** with allyltrimethylsilane in the presence of boron trifluoride etherate gave C-glucoside **4** in 72% yield with an α : β ratio of 1 : 1 in 1,2-dichloroethane, while the same reaction carried out in acetonitrile afforded C-glucoside **4** in 68% yield with an α : β ratio of 95 : 5 (Scheme I).[4]

Scheme I



Stereoselectivity may also be enhanced by changing Lewis acids. The boron trifluoride etherate promoted reaction of the silyl enol ether of acetophenone with O-(α-D-glucopyranosyl)-trichloroacetimidate **5** gave a 1 : 1 mixture of anomers **6** and **7** in 76% yield, while the zinc dichloride promoted reaction gave the α-C-glucopyranoside **7** in 73% yield as the only detectable diastereomer (Scheme II).[5]

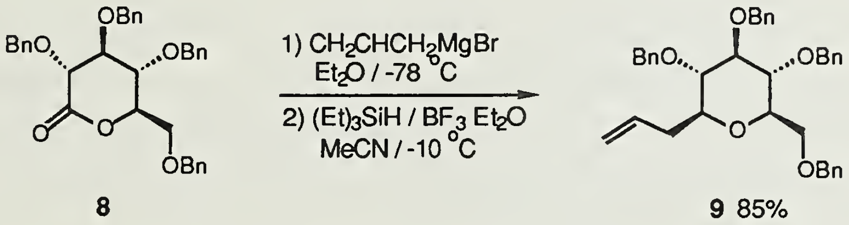
Scheme II



The formation of β-C-glycosides *via* an intermediate pyran oxocarbenium ion has also been accomplished by the reduction of hemiketals.[6] The 2,3,4,6-tetrabenzyl-glucopyranolactone **8** was treated with allylmagnesium bromide to give the hemiketal. The hemiketal was reduced with triethylsilane in the presence of boron trifluoride etherate to give the β-C-glycoside **9** exclusively

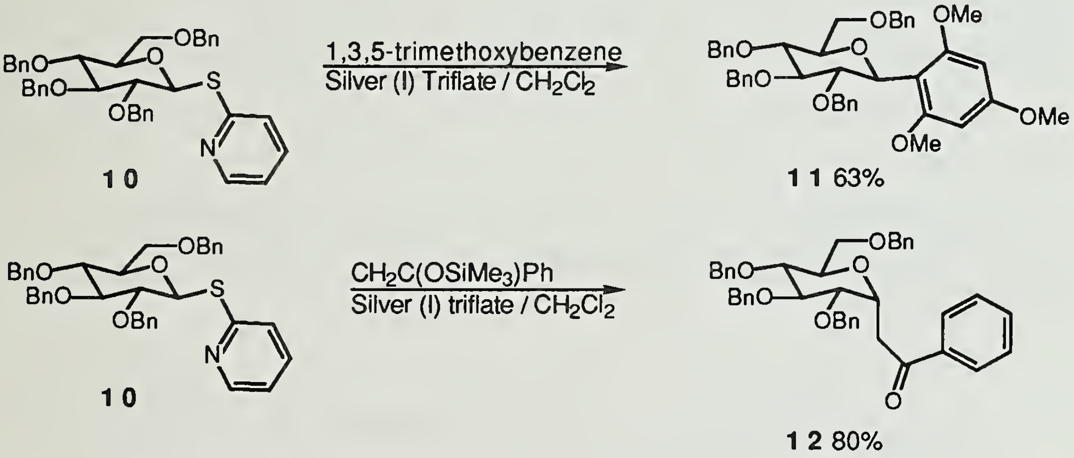
(Scheme III). Nucleophilic attack by hydride (H^-) from the α (axial) side on the initially formed oxocarbenium ion was suggested to explain the observed stereoselectivity.

Scheme III



Pyridyl thioglycosides have also been used in the stereoselective synthesis of C-glycosides.[7a,b] Silver (I) triflate promotes the loss of the thiopyridyl moiety to give either a solvent separated or an intimate oxocarbenium ion pair.[7a] The nucleophile 1,3,5-trimethoxybenzene in dichloromethane attacks pyridyl thio-β-glycosides **10** in the presence of silver (I) triflate to give β-C-glycosides **11** as the only diastereomer (Scheme IV).[7b] Trimethyl silyl enol ether nucleophiles in dichloromethane attack pyridyl β-thioglycosides **10** in the presence of silver (I) triflate to give α-C-glycosides **12** selectively (Scheme IV). The difference in selectivities between these two types of nucleophiles has been explained by a α / β-triflate intimate ion pair equilibrium. Highly reactive nucleophiles (1,3,5-trimethoxybenzene) are believed to trap the α-triflate ion pair before the more stable β-triflate ion pair can be established, resulting in the β-C-glycoside.

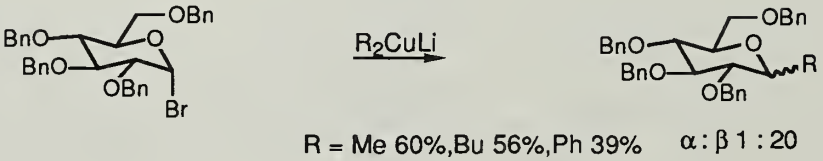
Scheme IV



Anomeric Substitution

A stereoselective synthesis of β-C-glycosides has been accomplished by an S_N2 substitution of α-glycosyl bromides by lithium dialkyl cuprates (Scheme V).[9] The yields are low (39-60%) and reported as not optimized, but the stereoselectivities are greater than 20 : 1. Elimination products are responsible for the low yields obtained in these cuprate reactions.

Scheme V



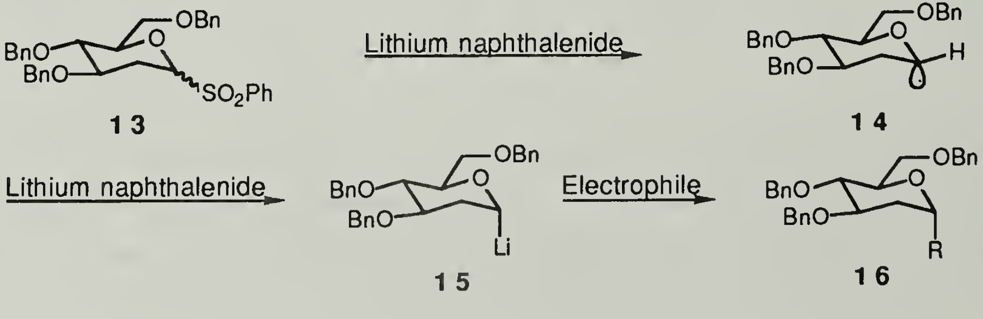
NUCLEOPHILIC ANOMERIC CENTER

Reactions that employ carbanionic (nucleophilic) character at the anomeric center of carbohydrates provide routes to either glycals (elimination) or anomeric mixtures of C-glycosides (substitution).[10a-c] Deprotonation at the anomeric carbon of sugars bearing strong electron withdrawing substituents at C-1 have been carried out with *n*-butyllithium or lithium diisopropylamide.[10a] The resulting lithium reagents are not configurationally stable and lead predominantly to an β-lithium reagent due to the anti-anomeric effect.[11b,c] Techniques which involve reductive lithiation and transmetallation have been developed in order to obtain configurationally stable glycosyllithium compounds.[13]

Reductive Lithiation

Homolytic cleavage of the carbon-sulfur bond of an anomeric mixture of 2-deoxy-glucopyranosyl phenylsulfones **13,** with one equivalent of lithium naphthalenide, gives an anomeric radical **14.**[10a] The resulting anomeric radical adopts an axial orientation in order to maximize overlap between its σ* antibonding orbital and the tetrahydropyran oxygen lone pair electrons and is selectively reduced with a second equivalent of lithium naphthalenide to afford a configurationally stable α-glycosyllithium reagent **15**. The lithium reagent selectively attacks various electrophiles such as methyl iodide, formaldehyde, acetaldehyde and deuterated water to give 2-deoxy-α-C-glycosides **16** in (43-80%) yield (Scheme VI).[11a-c]

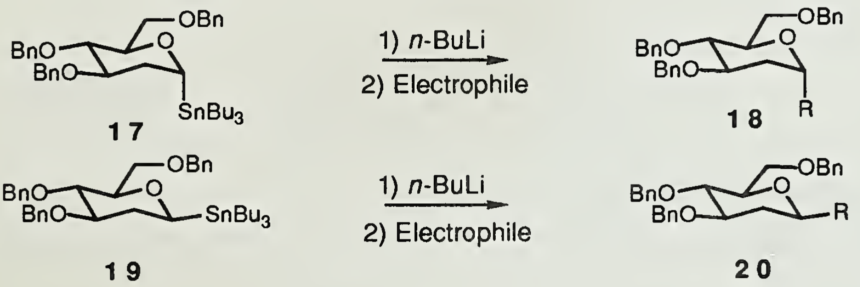
Scheme VI



Metal-Metal Exchange

Transmetallation of either α- or β-C-glycosylstannanes proceeds with retention of configuration and leads to configurationally stable glycosyllithium reagents.[12] Trapping of the glycosyllithium species by an electrophile also proceeds with retention of configuration leading to C-glycosides with overall retention of configuration.[13] Thus 2-deoxy-α-glucopyranosylstannane **17** reacts with various electrophiles such as acetaldehyde, isobutyraldehyde and deuterated water to give 2-deoxy-α-C-glucopyranosides **18** in (74-95%) yield, while 2-deoxy-β-glucopyranosylstannane **19** reacts with the same electrophiles to give 2-deoxy-β-C-glucopyranosides **20** in (74-95%) yield (Scheme VII).

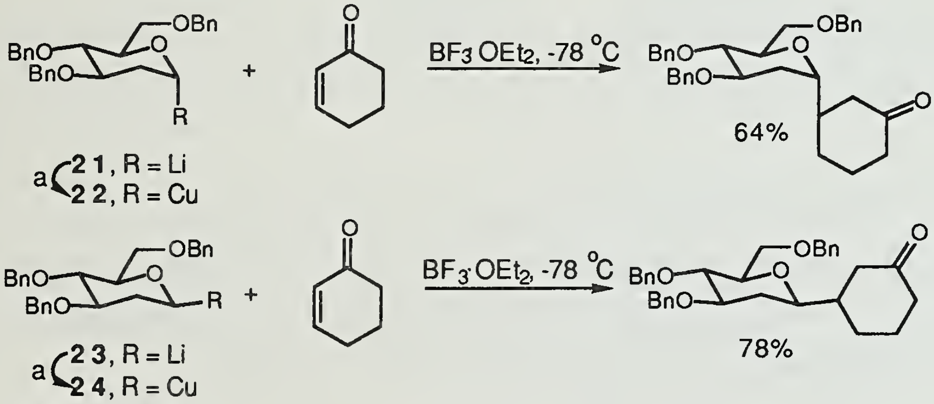
Scheme VII



Organocopper Reagents

The 2-deoxy α- and β-glucopyranosyllithium reagents **21** and **23**, which are prepared by transmetallation of the α- and β-glucopyranosylstannanes **17** and **19**, have been converted into α- and β-glucopyranosylcopper reagents **22** and **24** respectively.[14] These glucopyranosyl copper reagents undergo 1,4 addition to α,β-unsaturated carbonyls with retention of configuration at the anomeric carbon (Scheme VIII).

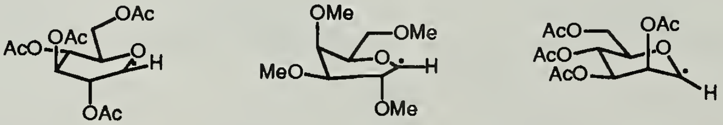
Scheme VIII



a) CuBr·Me$_2$S
DIPS-THF, -78 °C

RADICAL ANOMERIC CENTER

Synthesis of C-glycosides via a radical chain process provides a useful alternative to ionic processes. Radicals generated at the anomeric center of carbohydrates are trapped to give predominantly the α-diastereomer.[15] The selectivities in these reactions depend on the conformation of the regioselectively generated glycosyl radical.[16a] Electron spin resonance studies suggest that anomeric radicals generated from tetra-alkoxy pyranoses prefer to adopt a conformation that is dependent on the carbohydrate configuration.[16b] Glucosyl, galactosyl and mannosyl anomeric radicals prefer $B_{2,5}$ **25**, half chair **26** and a $^4C_1$ **27** conformation respectively (Figure 3).[17] These conformers are adopted in order to maximize the stabilizing interaction between the σ*-orbital (LUMO) of the β-C-OR bond and the unpaired electron at the anomeric center.[17]



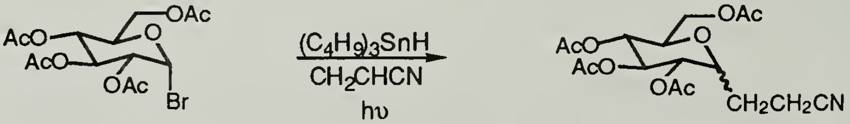
25 **26** **27**

Figure 3

Radical Chain Reaction

Photolysis of a solution of α-glucosyl bromide **28** in the presence of tributyltin hydride generates the glucosyl radical **25**, which when trapped with acrylonitrile, gives the α-C-glucoside **29** selectively (Scheme IX).[18] Acrylonitrile adds to the equatorial side of the glucosyl radical **25** in order to avoid a 1,3 diaxial interaction in the $B_{2,5}$ conformation.

Scheme IX

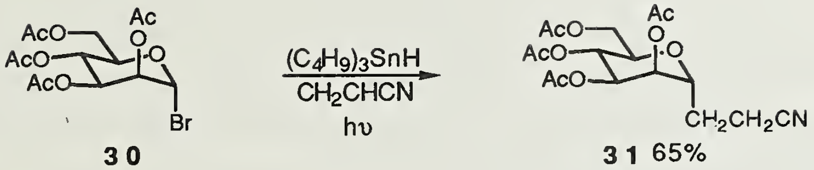


28 **29** 72%

α : β = 93 : 7

When a solution containing α-mannosyl bromide **30**, tributyltin hydride and acrylonitrile is photolyzed, selective formation of the α-C-mannoside **31** (via the mannosyl radical **27**) is accomplished (Scheme X).[18] Acrylonitrile adds to the axial side of mannosyl radical **27** in order to avoid a steric interaction with the axial C-2 alkoxy substituent.

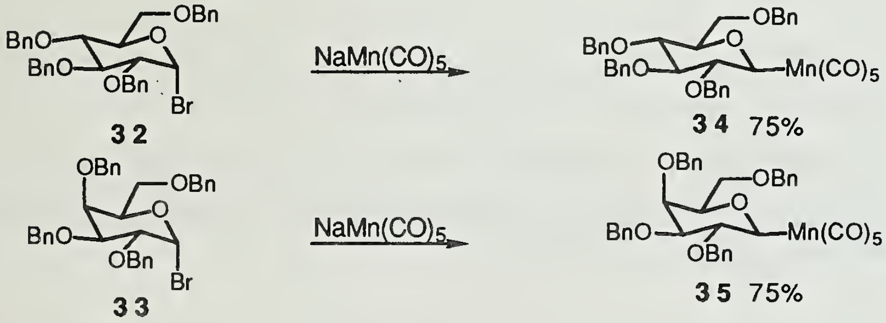
Scheme X



Organo-Transition Metal Approach

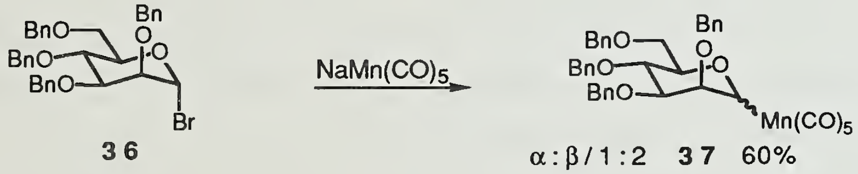
The condensation of sodium pentacarbonylmanganate(I) with α-glycosyl bromides has been shown to proceed with inversion of configuration at the anomeric center.[19] Both counter ion and the configuration of the C-2-alkoxy group have a dramatic effect on the stereoselectivities observed in these reactions. When α-glucosyl **32** and α-galactosyl bromides **33** were treated with sodium pentacarbonylmanganate(I) the only detectable products were the β-glucosyl **34** and β-galactosyl manganese pentacarbonyl complexes **35** respectively (Scheme XI).[19] When the glucosyl bromide was condensed with sodium pentacarbonylmanganate complex in the presence of tetrabutylammonium bromide the α-glucosylmanganese complex predominated while the same reaction in the presence of potassium bromide gave the β-glucosylmanganese **34** exclusively.[20]

Scheme XI



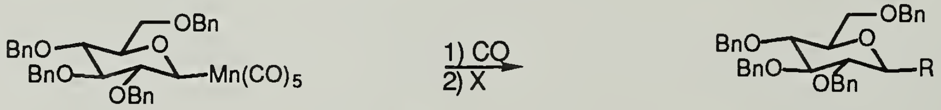
Condensation of sodium pentacarbonylmanganate(I) with α-mannosyl bromide **36** did not proceed with complete retention of configuration and a mixture of the mannosyl pentacarbonyl complex **37** was obtained (Scheme XII).[19]

Scheme XII



A migratory insertion of carbon monoxide in the pentacarbonylmanganese complex **34** proceeds with retention of configuration and the resulting acylmanganese complex is cleaved with methanol / sodium bicarbonate or sodium thiophenolate to give the corresponding esters **38** or **39** (Scheme XIII). Alternatively, the pentacarbonylmanganese complex **34** may undergo carbonyl insertion in the presence of methyl acrylate, which after photodemetalation of the resulting manganacycle, gives the γ-ketoester **40** (Scheme XIII).[19]

Scheme XIII



34

X = $^{-}$OMe, $^{-}$SPh, CH_2CHCO_2Me R = CO_2Me **38**, 63%, C(O)SPh **39**, 46%, $C(O)CH_2CH_2CO_2Me$ **40**, 47%

CONCLUSIONS

The syntheses of C-glycosides described above rely on the stereoelectronic effects at the anomeric center. The well known anomeric, anti-anomeric and reverse-anomeric effects are responsible for the conformation that the carbohydrates adopt during these reactions. The inherent electrophilic charcter of the anomeric center is well adapted for the synthesis of α-C-glycosides. While generation of stable α-or β-carbanions at the anomeric center has been accomplished, these nucleophiles cannot be generated with C- 2 alkoxy substituents. Radical generation at the anomeric center is the mildest of the three techniques and anomeric radicals of carbohydrates are well suited for the synthesis of α or β-C-glycosides.

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PALLADIUM CATALYZED CROSS-COUPLING REACTIONS OF ORGANOMETALLICS AND ORGANIC HALIDES: MECHANISM AND APPLICATIONS.

Reported by Joseph J. Schwab February 23, 1989

INTRODUCTION

The coupling of organometallic reagents with electrophiles (eq 1) represents one of the simplest and most useful reactions for the formation of carbon-carbon σ bonds. Several methods for the direct coupling of organometals with electrophiles are known, such as the Wurtz coupling[1] of alkyl halides and the coupling of Grignard or lithium reagents with alkyl halides. Copper catalyzed coupling[2] of organolithium compounds with alkyl or aryl halides has been successful, allowing the coupling of a wide variety of organic groups. However, while some of these reactions are useful the majority are severely limited by side reactions or by the types of organic structures which can be tolerated in either the organometallic reagent or the electrophilic group.

$$RM + R'X \longrightarrow R{-}R' + MX \quad (1)$$

Coupling reactions catalyzed by transition metal salts have been known for some time,[3] however, it was not until the early 1970's that significant developments in this area began. In 1972, Corriu[4] and Kumada[5] independently reported that nickel phosphine salts were capable of catalyzing the coupling of organometallic compounds with alkenyl and aryl halides. The high yields and stereoselectivity of the coupling stimulated much interest in the reaction. Palladium phosphine salts were later found to catalyze the reaction and have the added advantage of giving higher yields and greater stereoselectivity.[6]

In this paper, the general scope, mechanistic possibilities, and some applications of the palladium catalyzed cross-coupling reaction will be covered.

SCOPE OF REACTION

While magnesium was originally employed as the metal in RM (eq 1), the range of metals for RM has since been greatly expanded. The use of boron[7a], zirconium[7b], and aluminum[7c] have been particularly important since substituted alkenyl metals are easily prepared by hydro- or carbo-metallation of alkynes. Tin[8] reagents have been well studied and there use in several synthesis well

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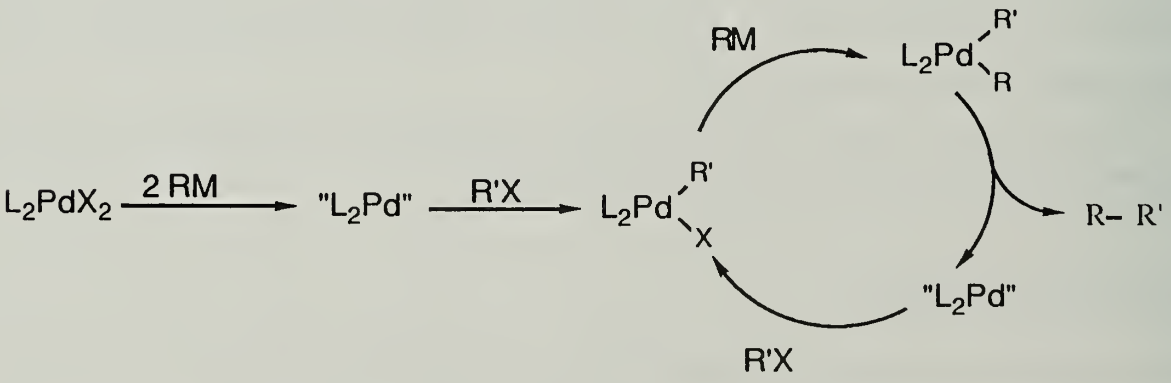
documented. Zinc[9] reagents have proved to be very effective in coupling reactions not only as the species RM but also as a secondary catalyst. Lithium[10] reagents suffer from competing lithium-halogen exchange with the organic halide, and in large excess they may inactivate the palladium catalyst by forming tetraorganopalladium complexes.[11] Several other metals such as Hg, Cd, Na, and K have also been examined.[12]

A wide variety of of organic groups in either RM or RX can be tolerated in the cross-coupling reaction. The organic group in RM can range from alkyl to aryl. Even allyl, homoallyl, and homopropargyl groups are coupled with certain metals. The organic group of RX can be alkenyl, alkynyl, or aryl. Most alkyl halides are unsatisfactory because of their low reactivity towards Pd^0 complexes.

MECHANISM OF CATALYSIS

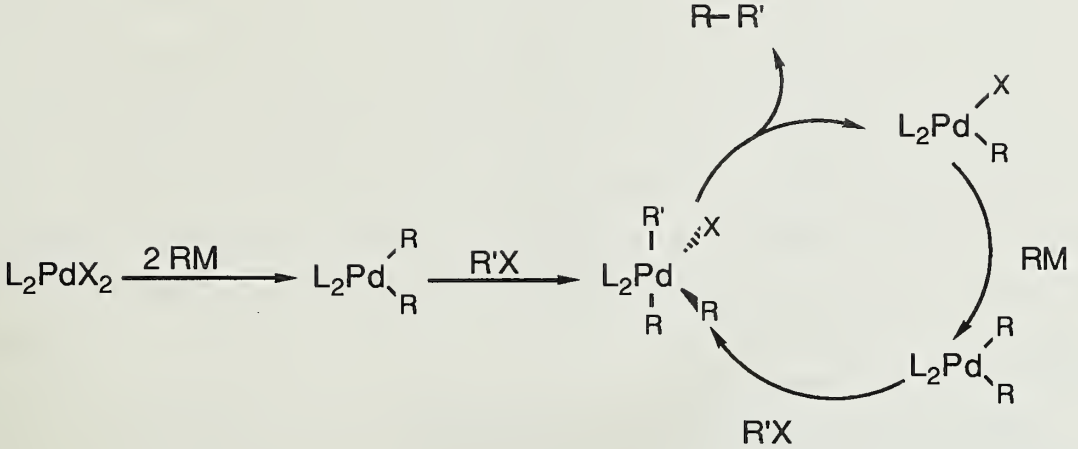
Scheme 1[13] represents a simple catalytic cycle for the palladium catalyzed cross-coupling reaction, based on generally accepted mechanisms for the individual steps. In the first step, the dihalobis(phosphine)palladium(II) precatalyst is reduced to a palladium(0) complex. Oxidative addition to the palladium(0) species is followed by transmetallation to give a dialkylbis(phosphine)palladium(II) complex. Reductive elimination of the cross-coupled product regenerates the palladium(0) which undergoes oxidative addition to complete the cycle.

Scheme I



Scheme 2[14] represents an alternative catalytic cycle which differs from Scheme I in that reductive elimination occurs from a palladium(IV) species. The different mechanistic possibilities in both cycles and the experimental evidence supporting each will be discussed.

Scheme II



The palladium catalyzed cross coupling reaction is believed to consist of three basic steps: 1) oxidative addition of an organic halide to palladium; 2) transmetallation of an organometallic to palladium and; 3) reductive elimination to give the coupled product. Each of the steps has requirements which must be included in any mechanistic proposal.

The active catalyst in the catalytic cycle is believed to be the coordinatively unsaturated "$L_2Pd(0)$" which is formed from the Pd(II) salt either by direct reduction using diisobutylaluminum hydride, or, in the case of alkylmetals, reduction by the organometal.[15] Presumably the "$L_2Pd(0)$" species can be formed *in situ* from alkylmetals by transmetallation of the L_2PdX_2 to give the L_2PdR_2 which then does a β-hydride elimination and reductive elimination. When tetraphosphinepalladium(0) complexes are used dissociation of one or two phosphine ligands is required.[16]

Oxidative addition of alkyl, alkenyl, and aryl halides to group VIII metals is well documented.[17] Three different modes of oxidative addition are possible: nucleophilic attack by the "L_2Pd" species; a radical chain process; or a concerted process. Nucleophilic attack in this case is improbable since S_N2 attack of this sort does not occur on vinyl systems. Radical chain processes are unlikely because isomerization of the olefin, expected if a vinylic radical formed and rapidly inverted, is not observed. Concerted addition of the organic halide via a three membered palladacycle would give retention of olefin configuration, which is observed.

Several mechanisms for the reductive elimination of R-R' from the dialkylpalladium complex are possible in this system. It is known that the two alkyl groups on palladium must be cis for reductive elimination to occur, and that reductive elimination occurs via a concerted mechanism with retention of configuration.[18] Reductive elimination from the square planar dialkylbis-

(phosphine)palladium(II) (L_2PdRR') complex can occur in one or more of the following ways: oxidative addition of a second equivalent of organic halide to the palladium(II) complex to give a palladium(IV), in which any of the three cis alkyl groups could eliminate; prior dissociation of a phosphine ligand to give a T-shaped palladium complex; or for complexes which contain at least one sp^2 bound carbon, by direct elimination from the square planar complex. Oxidative addition to a palladium(II) complex is known[19], however, the resulting palladium(IV) complex could reductively eliminate any of the three mutually cis ligands to give a mixture of cross-coupled products. Because addition to the palladium(II) is likely to be slow with respect to the other eliminations, and only one product is observed this is not a major route in most systems. The formation of T-shaped complexes or direct elimination are most likely the important product forming reactions in most systems.

Several factors can affect the transmetallation process in the catalytic cycle. Organic groups containing electropositive metals such as lithium or magnesium are expected to undergo rapid transmetallation because of the carbanionic nature of the organic group. However, use of these organometallic reagents can lead to the formation of "ate" complexes[11] which inactivate the palladium catalyst and result in lower turnover rates. Use of less electropositive metals such as tin and zinc leads to higher turnover rates. Presumably, "ate" complexes are not formed with the less reactive tin and zinc reagents.

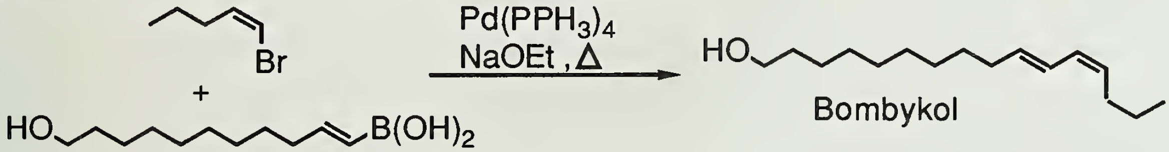
Reaction of the *trans*-L_2PdRX complex, isolated from the oxidative addition of an organic halide to a palladium(0) species, with organometallic reagents results in transmetallation to give the *trans*-L_2PdRR' species which is stable towards reductive elimination, and must undergo cis-trans isomerization to the cis in order to eliminate.[20] Several mechanisms for cis-trans isomerization are possible. Added phosphine has been shown to cause cis-trans isomerization in square planar complexes by forming a pentacoordinate palladium complex followed by pseudorotation and ligand dissociation.[21] Therefore, it is possible that excess phosphine dissociated during the reaction could catalyze the isomerization. Recent experiments have shown that when an organomagnesium such as CH_3MgI is used as the organometallic, cis-trans isomerization via a dimethylbis(phosphine)palladium can occur.[22]

The rate determining step in the catalytic cycle has proven difficult to determine and probably varies from system to system. Oxidative addition to the coordinatively unsaturated, or weakly solvated, palladium species "L_2Pd" is rapid.[23] Transmetallation can be rate limiting especially in the case of tin and zinc.[24] In other instances the reductive elimination could be rate limiting. mechanistic studies are complicated further by the fact that several mechanisms are possible for each step and that the mechanism may change with the type of substrate used.

APPLICATIONS

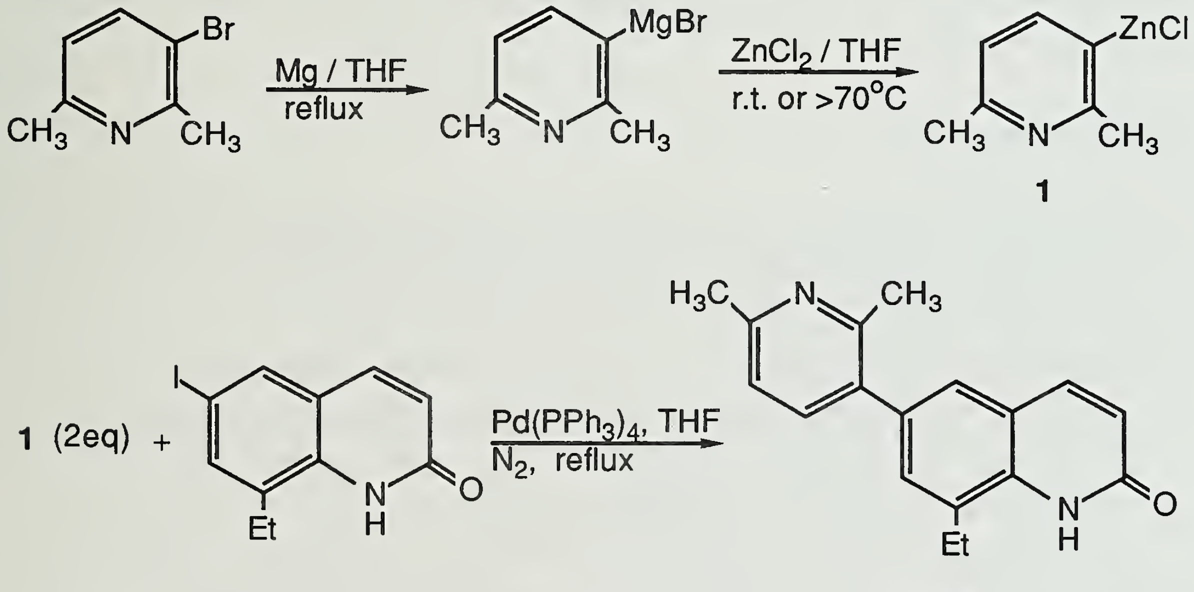
Several syntheses illustrating the ease and versatility of the palladium catalyzed cross coupling reaction have been conducted. The total synthesis of the pheromone Bombykol (from *Bombyx mori* L) and its three geometrical isomers has been accomplished by Suzuki, Suginome, and Miyura.[25](Scheme 3) The synthesis utilizes hydroboration of alkynes to prepare both the alkenyl halide and the alkenyl metal used in the cross coupling reaction. The palladium catalyzed final step gives bombykol in 82% (65% overall based on 10-undecen-1-ol) as compared to other synthesis which gave bombykol in less than 45% overall yield.

Scheme III



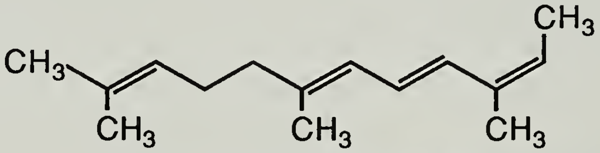
Roberts[26] *et al* used the palladium catalyzed coupling of pyridine derivatives and haloquinolines in a one pot synthesis of 6-pyridinyl-2(1H)-quinolines(2) in good to excellent yields.(Scheme 2) Syntheses of these potential cardiac stimulants prior to the present application involved the separate, multistep synthesis of either the 6-pyridinyl moiety or the quinoline system.

Scheme IV

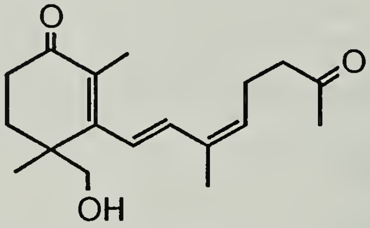


(2) 96%

Other workers have applied the palladium catalyzed cross coupling to the synthesis of 1,3 dienes and dieneones as exemplified by the synthesis of (+-)-Trisporl.[27] Terpenoid as well as sesquiterpenoid compounds have also been synthesized using this methodology as shown by the syntheses of α-farnesene[28] and *trans* (C_{10})-allofarnesene.[29] Kumada, using chiral ferrocenyl ligands, has successfully extended the reaction to asymmetric syntheses.[30]



trans (C_{10})-allofarnesene



(+-)-Trisporl

CONCLUSION

Since its discovery almost 20 years ago, much effort has gone into the study of the palladium catalyzed cross-coupling system. The cross-coupling reaction allows for the synthesis of many types of olefinic, acetylenic, and aryl species in high yields and stereochemically pure. A catalytic cycle has been proposed and used to study the scope and limitations of the reaction with respect to both coupling partners. The mechanistic aspects have also been studied, and while much has been learned, more work is still needed in the area of transmetallation and reductive elimination.

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STRUCTURE-ACTIVITY RELATIONSHIPS OF THE MONOBACTAMS

Reported by Stuart Bigham February 27, 1989

INTRODUCTION

The discovery of penicillin by Fleming in 1929 ushered in a new era in the fight against disease. For the first time researchers realized that many ß-lactam-containing compounds frequently possessed antimicrobial properties that could be of use in fighting infection. Since then, a great deal of effort has been put forth to isolate new ß-lactams in the hopes of obtaining compounds with increased potency.[1a,b] Because of this intensive effort, a host of new antibiotics have since come into general use.[2a,b] Yet, among these clinically useful antibiotics, there is suprisingly little structural variation (Figure 1). For some time, therefore, the premise was widely held that these fused ring templates were a necessary requirement for antibacterial activity.[3a-c]

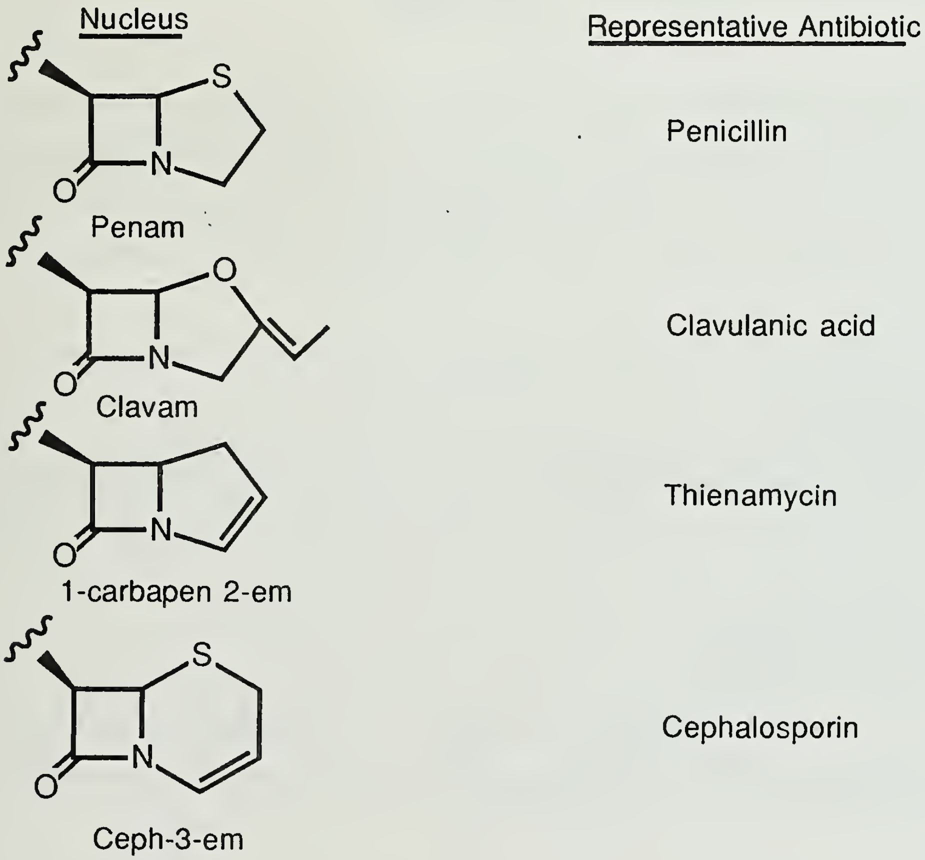

Figure 1

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With the advent of more sophisticated screening procedures, however, a totally new class of ß-lactams has recently been discovered. These monocyclic systems or "monobactams" (Figure 2) as they are called show only weak antibacterial activity; yet that they show activity at all is cause for one to reconsider the structure-activity relationships which exist among the ß-lactam antibiotics in general.[4a,b] Because the monobactams are quite simple systems, an exploration of their structure-activity relationships should provide a fundamental understanding of those factors which are responsible for the antibacterial properties of other ß-lactam antibiotics.

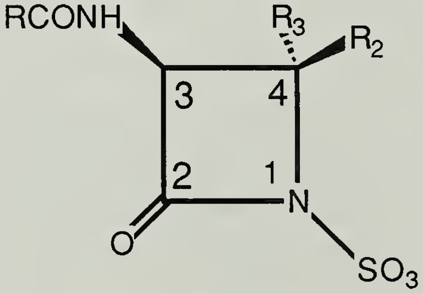


Figure 2

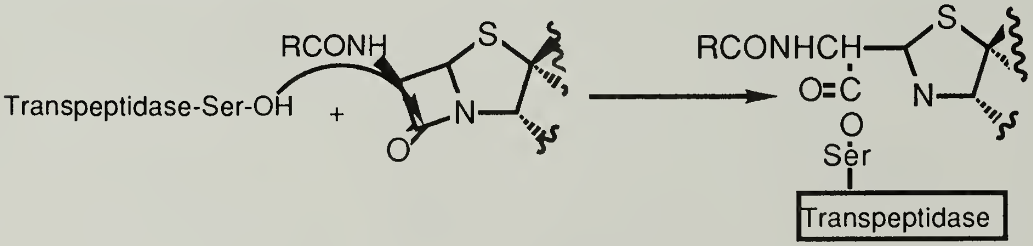
Before any such study can be undertaken, it is first important to define the mechanism by which these antibiotics inhibit bacterial cell growth. Studies have shown that the ß- lactams act by inhibiting the last step in cell wall biosynthesis, namely the crosslinking reactions, by forming a covalent intermediate at the active site of the peptidoglycan transpeptidase or crosslinking enzyme (Scheme 1).

Scheme I

Normal Reaction

$$\text{R'-Ala-CONH-Ala-COO}^- \xrightarrow[\text{- Ala}]{\text{transpep.}} \text{R'-Ala-CO-Enzyme} \xrightarrow[\text{Enzyme}]{\text{R-GlyNH}_2} \begin{array}{c}\text{R'-Ala-CONH-Gly-R}\\ + \\ \text{Enzyme}\end{array}$$

Reaction with ß-lactams



formed, the acylated enzyme is quite stable because it can not dissociate or dissociates very slowly.[5] Since the cell wall now lacks the reinforcement of the crosslinks, lysis occurs due to the high internal osmotic pressure and the cell is destroyed. Comparisons of x-ray crystallographic data[6] (Figure 3) plainly show why these antibiotics are recognized as substrates for the transpetidase which usually only recognizes the D-Ala-D-Ala tail of the nascent glycopeptide. Even though this resemblance is not perfect, the amide bond to be cleaved still occupies the same position as in the natural substrate. Therefore, ß-lactams are perceived to behave as transition state analogs in that they resemble the transition state attained on the reaction path leading to product. Other properties which influence inhibition by ß-lactams are permeability and resistance to lactamases produced by the target cell.[1a] Permeability refers to the ability of the antibiotic to pass through the cell wall of an organism. Once inside the cell, it is capable of binding the transpeptidase which seems to be anchored to the inner cell wall.[7] The antibiotic must also be resistant to lactamase, because without this resistance the ß-lactam would never reach the enzyme's active site intact. Lactamases "deactivate" the ß-lactam by catalyzing the hydrolysis of the amide bond. So as one seeks to modify the monobactams in order to increase antimicrobial activity, active site recognition must be increased and lactamase resistance and permeability maximized.

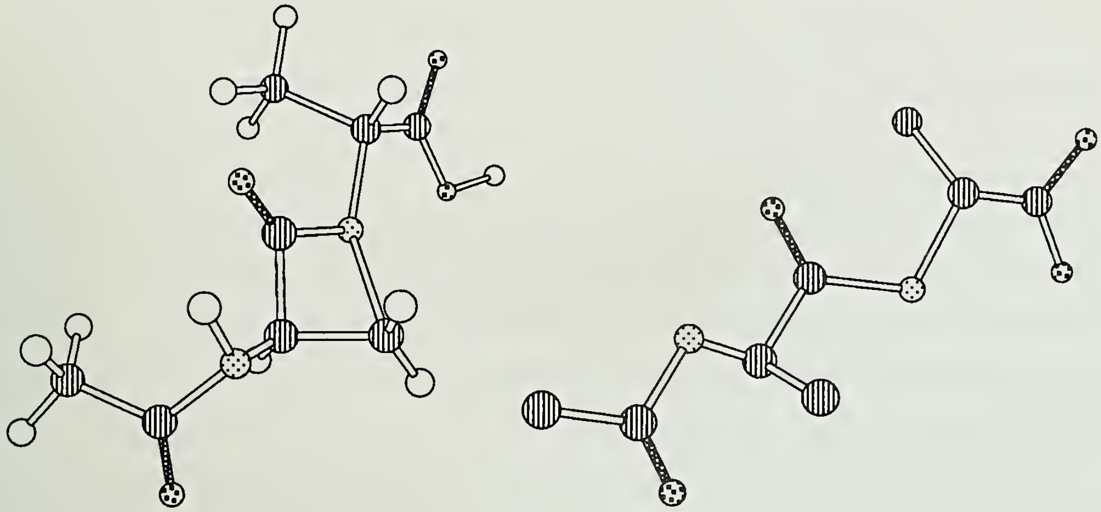
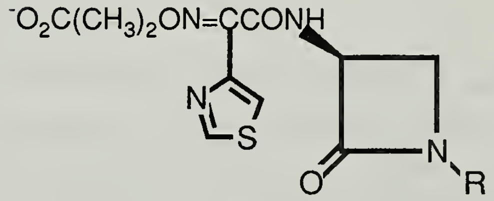


Figure 3

STRUCTURE-ACTIVITY RELATIONSHIPS

The first question that must be answered is by what process are the monobactams biologically activated toward a cell's crosslinking enzyme? In the penicillins for example, this activation is thought to be achieved by the bicyclic system which increases the strain of the four-membered ring, rendering it more suceptible to nucleophilic attack.[8] The presence of an electron withdrawing groups at points around the two-ring skeleton decreases electron density in the lactam ring thereby increasing chemical reactivity. These ground state properties are further enhanced prior to the attack of the nucleophile at the enzyme's active site as the two-ring system goes from its normal puckered conformation to one which is almost planar . This change in conformation enormously increases the strain in the ß-lactam and facilitates reaction with the enzyme nucleophile.[9] Increased chemical reactivity then seems to be a necessary requirement for biological activity. Being naturally flat, however, the monobactams must rely on mechanisms other than ring flattening to achieve activation. The solution seems to lie in the nature of the N-1 substituent. Introduction of different electronegative substituents onto N-1 confers varying degrees of antimicrobial activity (Table 1), whereas the absence of such groups produces monobactams which are totally devoid of biological response.[10] This leads to the conclusion that increased chemical reactivity is in part responsible for biological activity.[11] The enhanced reactivity is necessary but not sufficient for creating potent antibiotics because monobactams constructed without further elaboration of the basic nucleus show only low levels of activity against bacterial infection.[12] Once ring activation is achieved, other sites on the monobactam nucleus must be modified in order to realize the full potential of these compounds as highly specific antibiotics. It should be noted that an acylamido group at the 3-position has also

Table I



R	Minimum inhibitory concentration (MIC) (mg/l)
H	Totally inactive
SO_3^-	.4
OSO_3^-	.8
$(O_2POCH_3)^-$	6.3
$(O_3PCH_3)^-$	3.1

been found to be required in most cases[3b], (*vide infra*) and the preceeding conclusion is predicated by the presence of such a group. The effect of substitution at 3-position will be examined in a succeeding section.

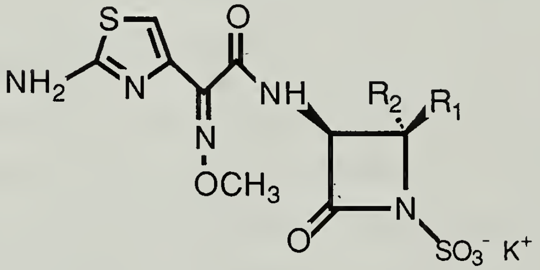
For any given monobactam skeleton, substituents at the 4-position seem to hold part of the answer of how to fine tune biological activity.[13] Indeed, different alkyl groups placed at this position produce dramatic changes in activity. These changes can not be simply ascribed to increased reactivity produced in the lactam ring because the alkyl groups share similar electronic properties. Furthermore, the effects of these groups differ greatly between gram positive and gram negative bacteria; and for this reason, discussion will be confined to gram negative strains. The distinction between gram negative and gram positive bacteria lies in the structural differences of their cell walls and in the variety and amount of polymers which are present. Gram-negative bacteria have cell walls which are highly structured and contain three distinct layers: the outer cell membrane, the inner cytoplasmic membrane, and a layer of peptidoglycan. These layers create a substantial permeability barrrier which must be overcome by any potential antibiotic. Gram-positive cells are not nearly as structured and contain less of a variety of macromolecules in their cell walls. Because they do not possess outer cell walls, gram-positive bacteria present much less of a permeability barrier to antibiotics. Introduction of a methyl group at the 4-position, for example, increases biological activity against gram negative bacteria such as *E. Coli* and stabilizes the compound against hydrolysis. Higher homologs (e.g. ethyl, propyl), show a concommitant decrease in biological activity accompanied by an increase in stability to destruction by lactamases. Finally, disubstitution of the methyl group results in ß-lactams which are much less active than the unsubstituted parent (Table 2), but are almost totally inert to lactamase catalyzed hydrolysis.[14] These results seem to indicate the importance of steric considerations and how these substituents interact with the target site of the enzyme.[14]

Stereoelectronic predictions concerning lactamases indicate that the enzyme-bound nucleophile should prefer to attack from the 2ß orientation where ß and α refer to topside attack and bottom-side attack respectively.[15] Disubstitution at the 3ß (*vide infra*) and 4ß positions should tend to inhibit this attack by blocking access to this face of the ß-lactam thus producing lactamase stability.[16] The observed increase in antibacterial activity may simply be a reflection of how well these groups aid in the positioning of the ß-lactam at the enzyme's active site or possibly that they serve to make the antibiotic more substrate-like in its three-dimensional appearance.

The 4-position holds only part of the answer of how to finely tune antibacterial activity. One must turn to an analysis of substitution the 3-position to more completely understand this process. As stated earlier, a minimal requirement for biological activity is the presence of an acylamido group at this position. Further, the acylamido function must exist in the S configuration, and best results are obtained when the 3 and 4 substituents are cis to one another.[14] This substitution pattern has previously been reconciled to trends in ß-lactamse stability but an explanation concerning biological activity also needs to be considered. Current data indicates that ß-lactam-enzyme binding is not at first a very ordered process.[17] There is a loose association between the two which becomes more ordered with time. It is thought that the 3-acylamido substituent (as well as the N-1 group) serves to position the ß-lactam more quickly in the proper orientation for reaction. Also, the 3-substituent has been implicated as a "molecular handle" which serves to distort the ß-lactam once bound to enormously increase its chemical reactivity.[18]

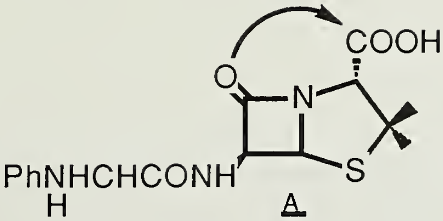
Aside from the affects of substituents at various centers around the monobactam nucleus, there also seem to be certain geometrical requirements for antibacterial activity. In a study by Cohen[19], x-ray crystallographic data were used to compare the structures of active and inactive penicillins and cephalosporins. Although strictly emperical, the observations are quite surprising. Biological activity is proposed be defined in terms of cones of orientation of the acidic group attached to the ß-lactam nucleus (Table 3). Overall, the distance between the oxygen of the ring amide bond and the carbon of the acidic group is shorter in the active compounds. In general, distances below 4 Å yield active structures, while those above 4 Å yield inactive ones. Furthermore, if the compound's acidic group is able to pseudorotate into this orientation, there is a strong tendency for it to do so and express its biological activity. As a part of a later test, this geometrical requirement was also found to hold for the monobactams. This gives a picture of the ß-lactam binding site as highly specific in its three-dimensional requirements. These observations point out that inactivity may be more a case of nonrecognition than reduced reactivity of the lactam ring.

Table II

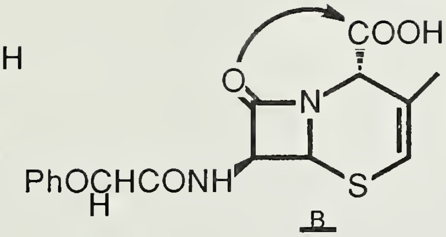


R_1	R_2	MIC (mg/l)
H	H	.8
CH_3	H	.1
H	CH_3	.1
CH_3	CH_3	25
CH_3CH_2	H	.4
H	CH_2CH_3	.4
$CH_3(CH_2)_2$	H	1.6

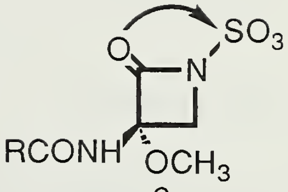
Table III



A



B



C

	A	B	C
DISTANCE(Å)	3.899	4.111	3.355
INACTIVE (I) ACTIVE (A)	A	I	A

The fruits of structure-activity considerations are apparent in the monobactam Aztreonam (Figure 4) which is currently in clinical use.[20] Its potent antimicrobial activity against only gram negative bacteria sets it apart from other ß-lactam antibiotics. In addition, it is resistant to the common lactamases; and this combination of potency and resistance makes Aztreonam more powerful than many of its ß-lactam relatives. All of the structure-activity relationships found have been taken into account in the construction of this compound.

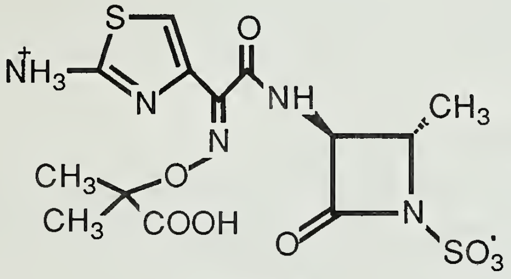


Figure 4

SUMMARY

The structure-activity relationships which exist among the monobactams and which determine their biological properties are a complex mixture of steric, stereoelectronic, and geometrical factors. No one explanation is satisfactory as to why these seemingly simple systems can exhibit potency toward gram negative bacteria and be virtually ineffective against gram postive strains. Even small amounts of antimicrobial activity is cause for one to reformulate the concepts which attempt to rationalize the mechinisms by which the ß-lactams as a family operate. It is hoped that by studying the monobactams that at least the minimal requirements for biological activity can be elucidated and that these requirements can serve as a starting point in the construction of new antibiotics.

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SYNTHETIC APPROACHES TOWARD THROMBOXANES

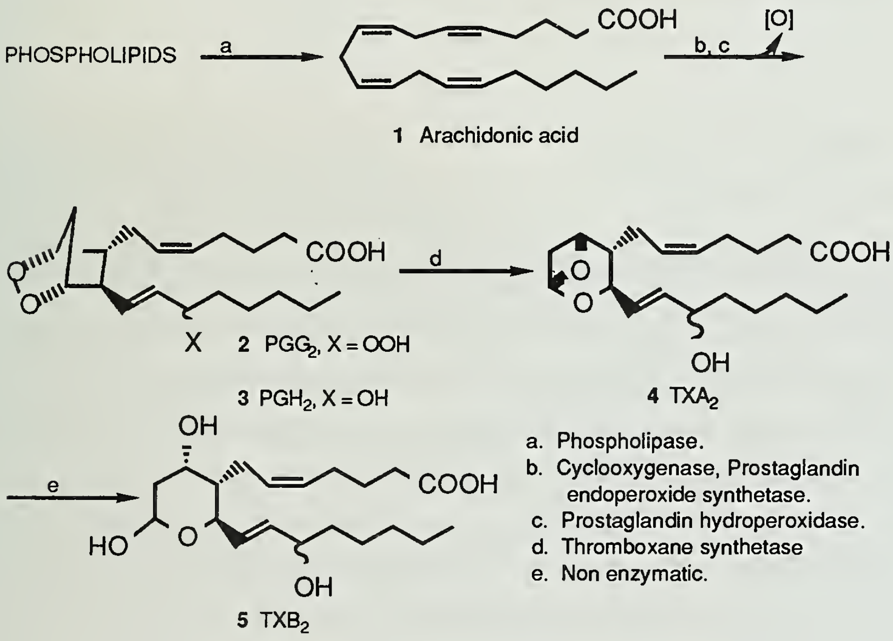
Reported by Ranjan J. Rajapakse

March 2, 1989

INTRODUCTION

During the past two decades great advances have been made in our knowledge of a group of biologically active compounds called eicosanoids, which are derived from arachidonic acid and include prostaglandins, prostacyclins, thromboxanes and leukotrienes[1]. Arachidonic acid is hydrolyzed from cell membrane phospholipids by phospholipase and then transformed into eicosanoids via the cyclooxygenase (Scheme I) and lipoxygenase pathways[2,3].

Scheme I



a. Phospholipase.
b. Cyclooxygenase, Prostaglandin endoperoxide synthetase.
c. Prostaglandin hydroperoxidase.
d. Thromboxane synthetase
e. Non enzymatic.

The isolation of the endoperoxides[4,5], prostaglandin G_2 (PGG_2) and prostaglandin H_2 (PGH_2), led to the discovery of two other very potent, unstable eicosanoids. In the conversion of thromboxane B_2 (TXB_2)[6,7] in platelets, an extremely unstable intermediate, thromboxane A_2 (TXA_2), was detected by trapping experiments[8]. It is an extremely potent platelet aggregator, broncoconstrictor and vasoconstrictor with very short half life[8].

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The structure presently accepted was originally proposed as a strained bicyclic acetal having a 2,6-dioxabicyclo[3.1.1]heptane skeleton on the basis of trapping studies and radiolabelling experiments[8]. Confirmation of the structure of TXA_2 by chemical synthesis has only recently been achieved[9].

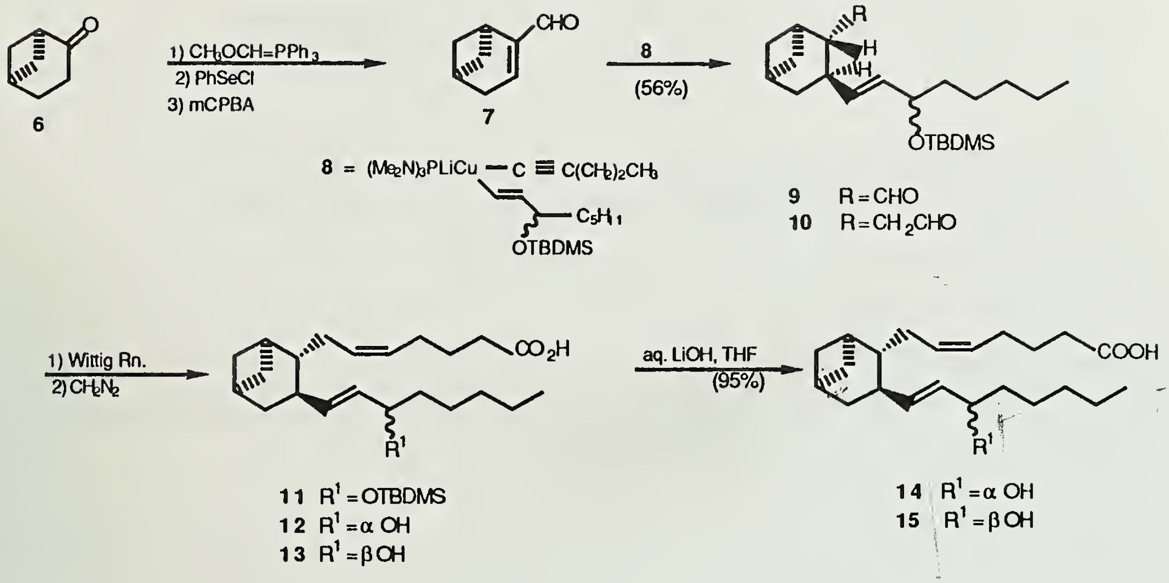
Since the first total synthesis of TXB_2 by Nelson *et al.*[10] in 1976, several syntheses have been reported[11]. In view of the supposed difficulty in the formation of the requisite ring system and the facile hydrolysis of TXA_2 to TXB_2, the search for TXA_2 analogs has centered on the synthesis of ring-modified compounds. In most of the TXA_2 analogs described to date one or both oxygen atoms in the 2,6-dioxabicyclo[3.1.1]heptane ring system have been replaced by carbon [12-24] or sulfur [25-31] or nitrogen atoms[32]. Among thromboxanes, TXA_2 shows the highest biological activity[33] as well as the greater synthetic challenge, and for these reasons the syntheses of TXA_2 and its analogs will be discussed here.

CARBOCYCLIC ANALOG OF TXA_2

Bicyclo[3.1.1]heptane Skeleton

Nicolaou *et al*[12] synthesized the strained bicyclo[3.1.1]heptane skeleton of carbocyclic analog(CTA_2) using two approaches. In the first approach bicyclo[2.1.1]hexan-2-one was ring expanded via a β-oxidocarbenoid intermediate. The regio isomer **6** was isolated in a ratio of 6:1 (Scheme II). The strategy for the second approach was to construct an appropriately functionalized six-membered ring and then at a convenient stage in the synthesis, use a displacement reaction to complete the bicyclic system. This was accomplished via the cyclization of the tosylate derived from 4-hydroxymethylcyclohexanone.The synthesis was continued as shown in scheme II via the unsaturated aldehyde, which allowed conjugate addition of the resolved ω-chain moiety. The α-side chain of CTA_2 was completed by homologation of the aldehyde function followed by Wittig reaction of **10**. Removal of the silyl group followed by chromatographic separation afforded diastereoisomers **12** and **13,** which on base hydrolysis gave the target molecule **14** and its hydroxy epimer **15**. CTA_2 exhibited extremely potent vasoconstricting activity[12]. However it behaved as a potent TXA_2 antagonist[12].

Scheme II

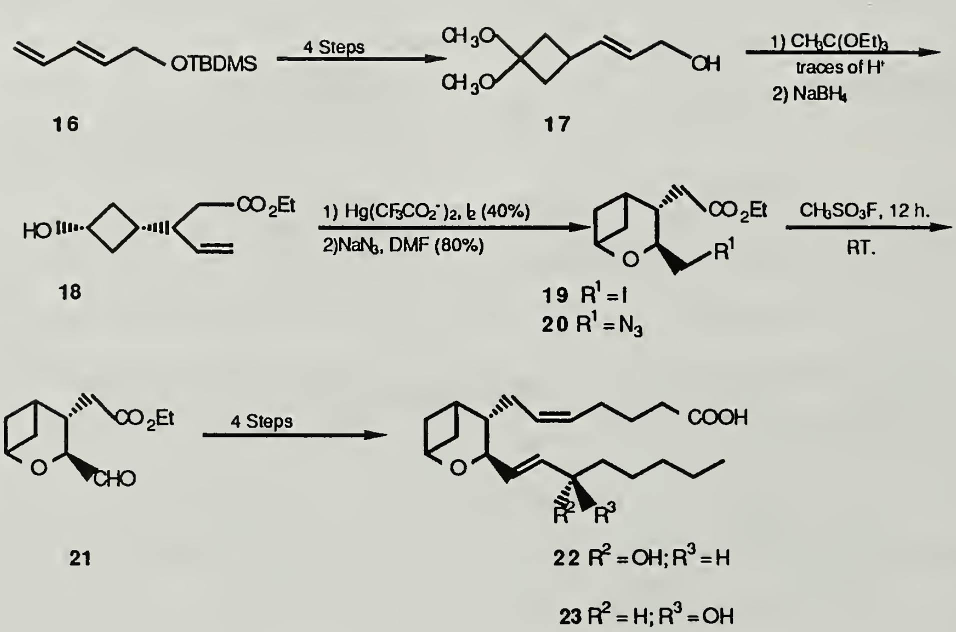


ETHER ANALOG OF TXA$_2$

2-Oxabicyclo[3.1.1]heptane Skeleton

A total synthesis of a TXA$_2$ analog in which one of the oxygens in the bicyclic nucleus is replaced by carbon was reported by Corey[19]. The construction of the required bicyclic ether from a four-membered ring precursor was the method of choice in this synthesis (Scheme III). Hydroxy ketal **17** was obtained from olefin **16** by using a series of routine reactions. Claisen rearrangement of **17**, followed by sodium borohydride reduction afforded cis alcohol **18** which was the key precursor for Corey's cyclization reaction. This was achieved by treatment of **18** first with mercury(II) trifluoroacetate in benzene followed by iodine. The synthesis of the aldehyde **21** that was used to form the α-side chain was accomplished by treating the azido ester **20** with methyl fluorosulfonate The TXA$_2$ analog **22** showed to be a powerful agonist on TXA$_2$ receptors[19].

Scheme III

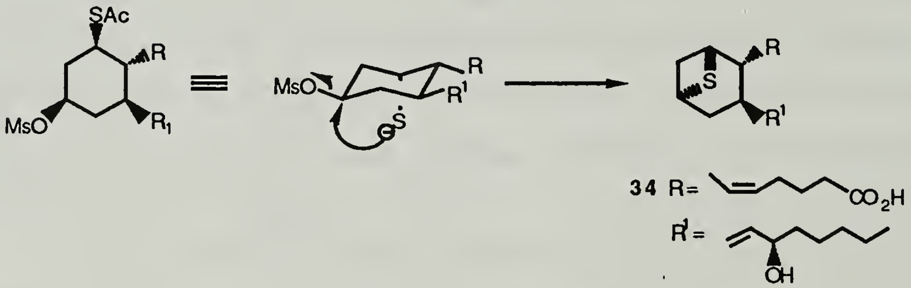


SULFUR ANALOG OF TXA_2

6-Thiabicyclo[3.1.1]heptane Skeleton

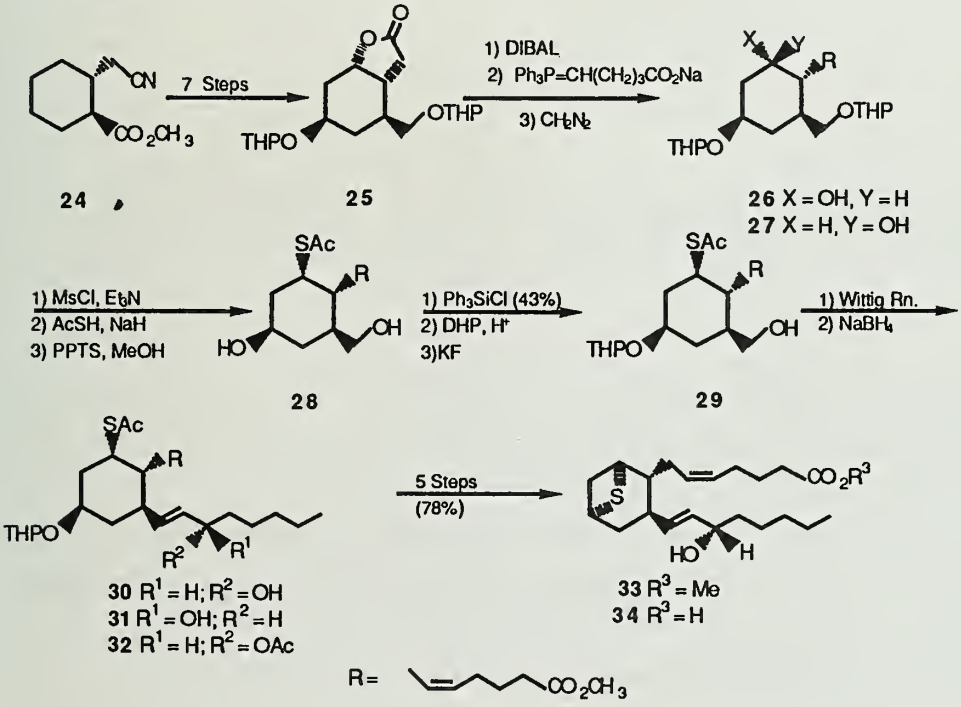
Hamanaka *et al.*[27] have achieved the first total synthesis of a TXA_2 analog possessing the 6-thiabicyclo[3.1.1]heptane skeleton, (±)-11a-methano-9,11-thia-TXA_2 **34**. Considering the procedure of Birch[34], Hamanaka realized that the required thietane ring could arise via an intramolecular S_N2 reaction (Scheme IV) of a suitably functionalized precursor.

Scheme IV



The compound **25** (Scheme V) was chosen as the key intermediate which had the functionalities necessary not only to lead to the precursor for the formation of the thietane ring but to extend two side chains. The synthesis of **25** began with a Diels-Alder reaction of butadiene and methyl (E)-4-oxobutenoate. The *trans*-1,3-diol system on the cyclohexane ring of **25** was introduced at this stage by iodololactonization of **24.** Conversion of the C-9α-alcohol functionality in **26** into a thioacetate with retention of configuration was accomplished via the C-9β-alcohol **27**. Prior to the formation of the ω-side chain, the distinction between the two hydroxy groups in **28** was achieved using suitable protection-deprotection manipulations. Following the procedure of Corey[35], the extension of the ω-side chain was completed. Mesylation of the selectively deprotected **32**, followed by treatment with sodium methoxide completed the synthesis of thietane ring. Both **34** and its C-15 epimer showed potent contractile activity but only **34** induced aggregation of human platelets in rich plasma, indicating the effective agonist activity.[27]

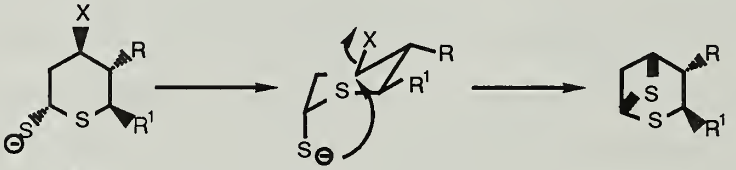
Scheme V



2,6-Dithiabicyclo[3.1.1]heptane Skeleton

The first total syntheses of racemic dithiathromboxane A_2 analogs were accomplished by Hamanaka and co-workers in 26 steps[30]. Six-membered precursor **35** with the stereochemistry shown in Scheme VI was chosen for the synthesis of the bicyclic thiane-thiatane moiety by intramolecular S_N2 reaction.

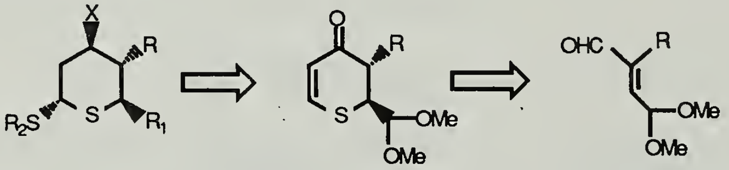
Scheme VI



35

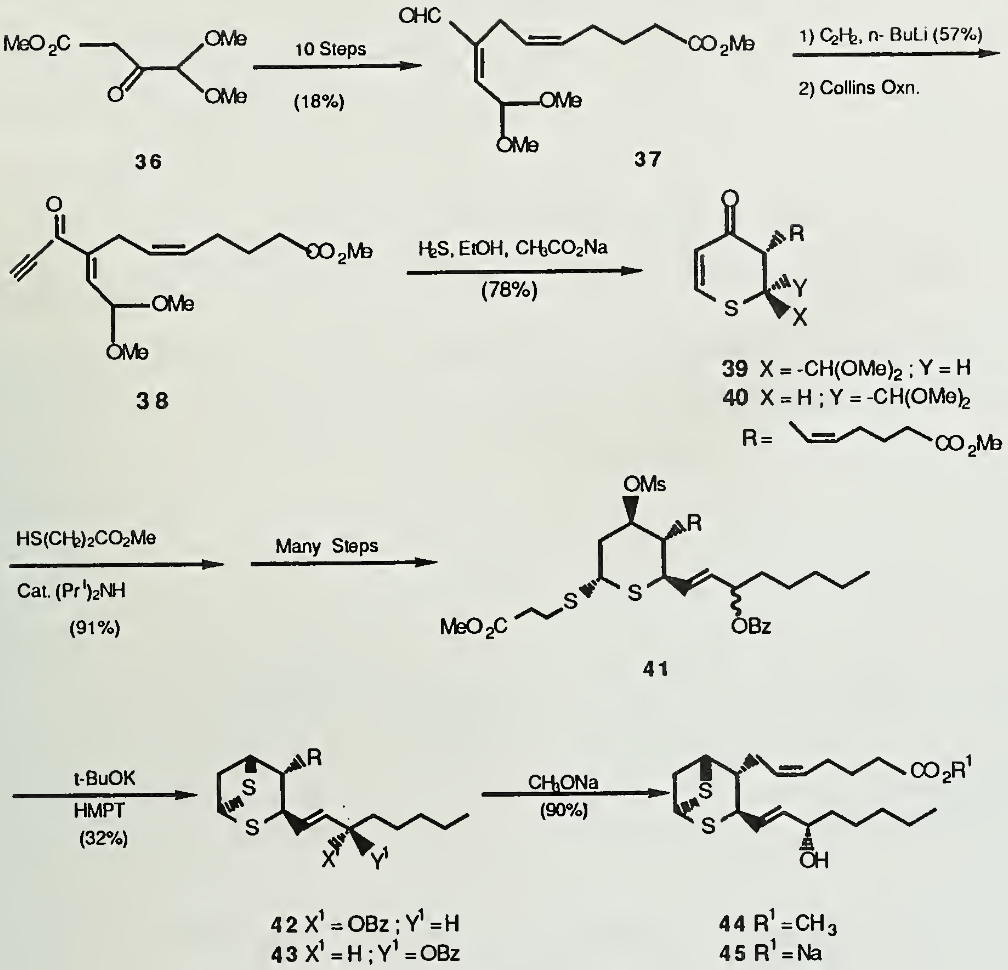
The precursor **35** (Scheme VII) was considered to be derived from the thiapyran derivative by stereoselective conjugate addition of a functionalized thiol, which in turn could be obtained from the aldehyde.

Scheme VII



The synthesis of the aldehyde **37** (Scheme VIII) was achieved from methyl-4,4-dimethoxyacetoacetate in 10 steps using routine chemical reactions. Treatment of **37** with lithium acetylide, followed by Collins oxidation furnished the acetylinic ketone **38**. This substance was converted to **39** by treatment with hydrogen sulfide. The second sulfur atom was introduced into the system with proper stereochemistry via the conjugate addition of 3-mercaptopropionate. Treatment of **41** with potassium-*t*-butoxide afforded the intramolecular cyclization products **42** and **43** in 21% total yield. The analog **45** proved to be one of the most potent agonist on TXA_2 receptors[30].

Scheme VIII



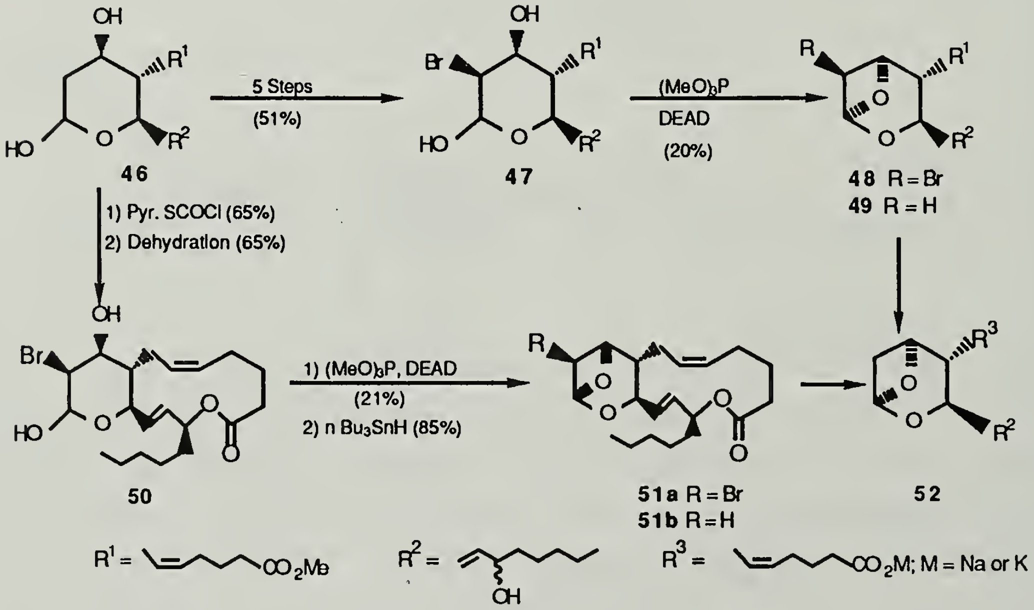
TOTAL SYNTHESIS OF TXA_2

2,6-Dioxabicyclo[3.1.1]heptane Skeleton

In 1985, Still [9] reported the first total synthesis of TXA_2 starting with commercially available TXB_2 methyl ester (Scheme IX). The key step in Still's synthesis of TXA_2 is the modified Mitsunobu reaction[36] which involves intramolecular dehydration. Key precursor **47** was synthesized from TBX_2 methyl ester in 5 steps. Treatment of **47** with diethyl azodicarboxylate and triethylphosphite gave desired bicycloderivative **48** in 20% isolated yield.

Hydride reduction of **48** afforded a material, in which the C-13, C-14 olefin had been lost, rather than the simple reduction product **49.** The approach of the C-10 radical to the C-13, C-14 olefin during the hydride reduction was anchored by forming 1,15-macrolactone **50.** The synthesis of **50** was accomplished by formation of thiopyridyl ester of **46**, followed by dehydration with Mukaiyama reagent[37] and immediate formation of bromohydrin. Modified Mitsunobu cyclization of **50** gave 10-bromo TXA_2 derivative **51a** in 21% isolated yield. Reduction of **51a** with polymer bound tin hydride gave the 1,15-anhydro- TXA_2 **51b** in very high yield. Sodium and potassium salts of TXA_2 **52** were obtained from **51b** by saponification and synthetic **52** was found to be indistinguishable from natural TXA_2 by their comparative potency in aggregating human platelets[9].

Scheme IX



SUMMARY

In addition to its important biological properties, thromboxane A_2 has served as a challenging target molecule to synthetic organic chemists. To circumvent the chemical instability of TXA_2, several analogs have been synthesized. None of these analogs, however, display the biological profile of the natural material. The total synthesis of TXA_2 by Still and co-workers provides strong evidence that the Samuelsson oxetane structure for TXA_2 is correct. This synthesis should also lead to the preparation of radiolabeled TXA_2 by utilizing tin tritiide in the final reduction step.

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TUMOR PROMOTORS: STRUCTURES AND THEIR BIOLOGICAL ACTIVITIES

Reported by Ryuichi Sakai March 9, 1989

Two stage carcinogenesis is now widely accepted as a mechanism of chemical neoplastic transformation which involves two different stages, referred to as initiation and promotion.[1] Compounds responsible for the first stage are called initiators and they bind to DNA covalently and irreversibly after metabolic activation.[2] The second stage is transformation of an initiated cell to a tumor cell. Carcinogenic compounds generally have the ability to both initiate and promote tumor cell formation (complete carcinogen), while tumor promoter compounds themselves are not carcinogenic and are involved only in the second stage. Unlike initiators, promoters do not bind to DNA and the promotion stage is reversible, suggesting that promoters interact with receptors noncovalently.[1b] A variety of compounds have been identified as tumor promoters, and of these, the diterpene esters (**1-4**), represented by 12-O-tetradecanoylphorbol-13-acetate (TPA, **1a**), the acetogenic polyether aplysiatoxins (**5**), and the indole alkaloid teleocidins (**6-13**) are known as the most potent skin tumor promoters.[3] These compounds are all categorized as TPA-type promoters because they have been shown to bind to the same receptors in cells. Recent work has focused on determining the structual features of these compounds responsible for their activities. This may lead to the ability to predict tumor promoting activities of environmental chemicals, the design of synthetic promoters, and characterization the receptor to study the mechanism of two stage carcinogenesis at the molecular level.[4]

BIOLOGICAL ACTIVITIES

TPA type tumor promoters have several characteristic biological activities. The most important is the in vivo two-step tumor promoting activity in mice skin,[1] but more sensitive and faster in vitro assays have also been developed. For example, adhesion of human promyelocytic leukemia cells (HL-60),[5a] mouse ear irritation,[5b] induction of differentiation of HL-60 cells,[5c] activation of protein kinase C,[5d] ornithine decarboxylase induction, and [^{3}H]TPA binding assay [5e,f] have all been developed and used. All these assays correspond well to in vivo assays and the last two assays have been used frequently to screen and test tumor promoters.

DITERPENE ESTERS

Diterpene esters isolated from the families Euphorbiaceae and Thymelaeaceae as irritant or toxic components have been shown to have strong tumor promoting activity in the mice skin

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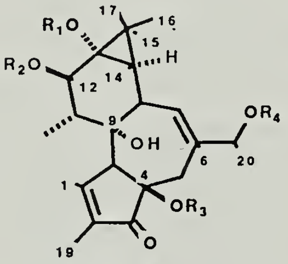
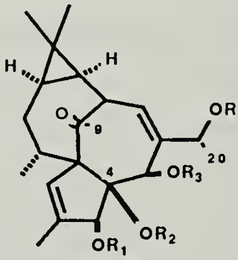
assay.[3a] These compounds are classified mainly into three different types of diterpenes, tigliane, ingenane and daphnane. And corresponding alcohols phorbol (**1b**), ingenol (**2b**) and 5-β–hydroxyresiniferonol (**3b**) are the parent alcohols of the esters.[6] The structures, including the absolute stereochemistries of these alcohols were determined by X-ray diffraction.[7] The active constituents always have long chain acyl groups and the parent alcohols themself have no tumor promoting activities. The structure-activity relationships of these compounds have also been studied using natural or semi-synthetic derivatives.[8] Structure-activity studies have indicated that the long chain acyl group (C_{10} - C_{16}) is required, although strict structural specificity was not seen.[4a-e] The primary hydroxy group on C-20 is indispensable.[4a-e] Conformation or molecular shape is also important because the modification which may alter them (C-4 epimer **4**, modified double bonds **1e**) cause the loss of activities [4a] (Figure 1).



phorbols

1a (active): R$_1$ = Ac,
R$_2$ = tetradecanoyl
R$_{3\text{-}4}$ = H

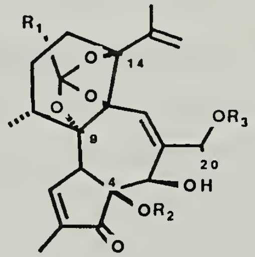
1b (inactive): R$_{1\text{-}4}$ = H
1c (inactive): R$_{1\text{-}3}$ = H, R$_4$ = Me,
1d (Inactice): R$_{1\text{-}2}$ = Ac, R$_{3\text{-}4}$ = H



ingenols

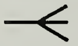
2a (active):
R$_1$ = tetradecanoyl
R$_{2\text{-}4}$ = H

2b (inactive): R$_{1\text{-}4}$ = H

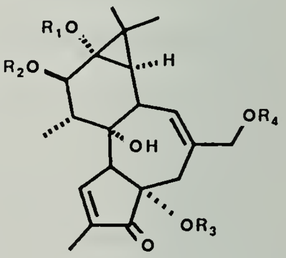


5-hydroxyresiniferonol-type

3a (active):
R$_1$ = hexadecanoyl
R$_{2\text{-}3}$ = H
3b (inactive):

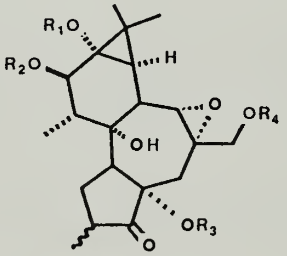
R$_1$  = 3H

R$_{2\text{-}3}$ = H

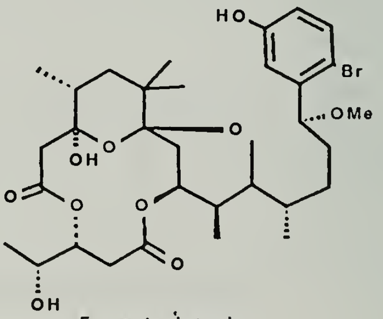


4-epi-phorbol

4 (inactive): R$_1$ = Ac
R$_2$ = tetradecanoyl
R$_{3\text{-}4}$ = H



1e: R$_{1\text{-}4}$ = H
(inactive)



5: aplysiatoxin

Figure 1

TELEOCIDINS

Another class of TPA-type tumor promoters are the indole alkaloid teleocidins and related compounds.[3b, 4a, 9] Teleocidins were first isolated from the fermentation broth of *Streptomyces mediocidicus* as a strong irritant.[10] The structure, including the relative stereochemistry of one of the teleocidins (B-2, **6b**) was determined by X-ray crystallography.[11] So far, more than twenty related compounds have been found from either *Streptomyces* spp. or the marine cyanobacteria *Lyngbya majuscula*.[12] The structure-activity relationships of these natural compounds have been elaborated (Figure 2).[4a, 13a-e].

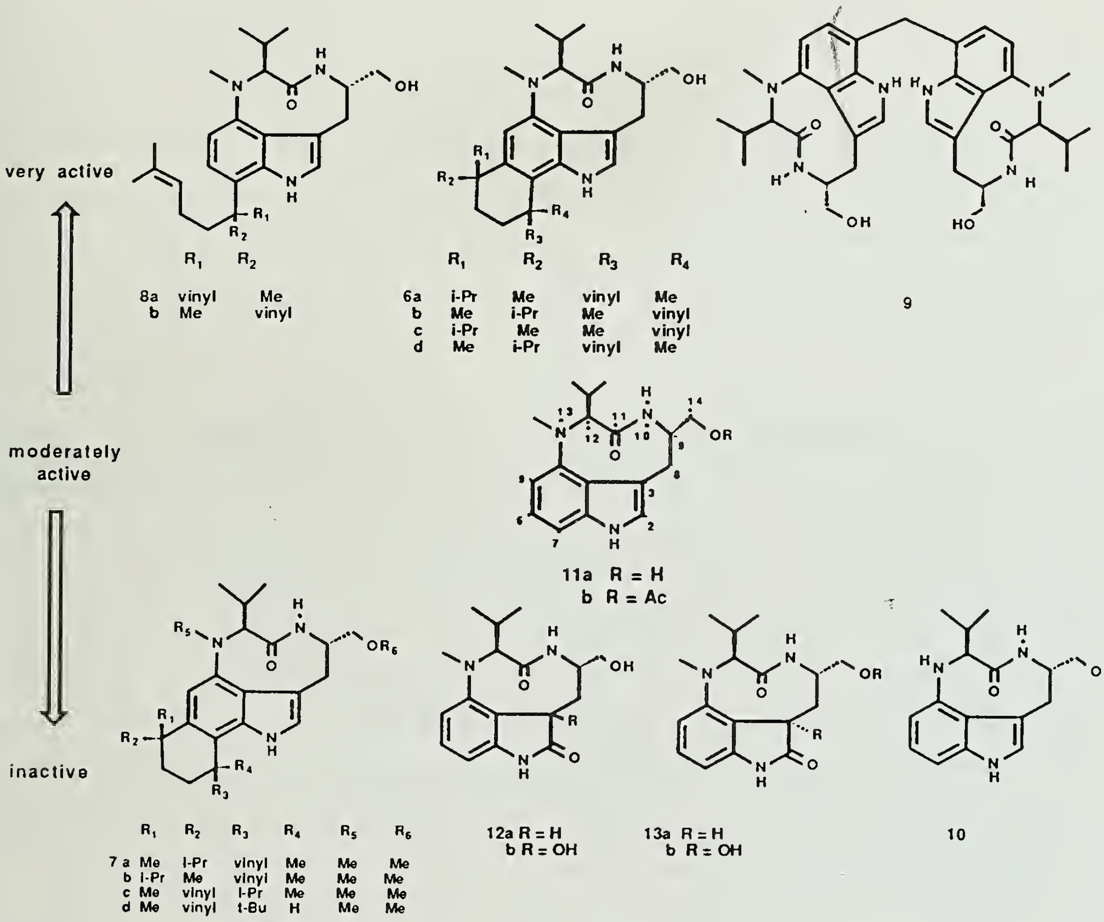
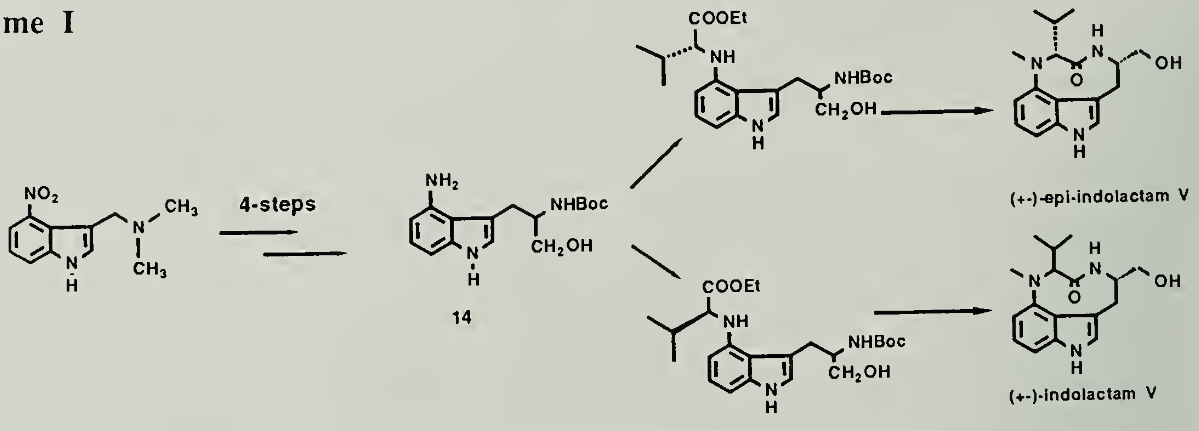


Figure 2

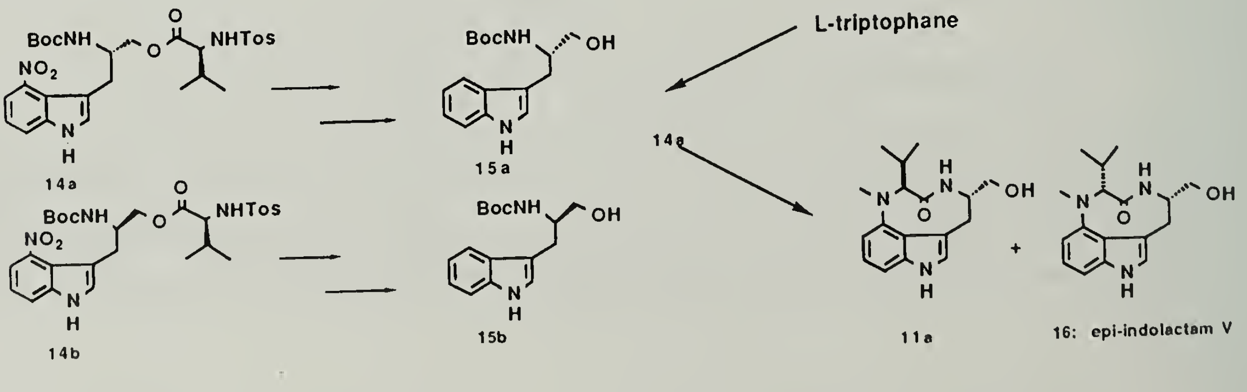
Oliviortins (**7a-d**), 14-O-alkyl derivatives isolated from *S. olivoreticuli*, were not active which clearly indicate that free hydroxymethyl group is important. The C-7 or C-6 and -7 substituted derivatives, teleocidin A-1, 2 (**8a, b**), B-1-4 (**6a-d**), biastmycetin A (**9**) isolated from *Streptoverticillium blastmyceticum* showed very strong activity, suggesting that the C-7 substituents substantially amplify the activities although the structural or stereochemical preference have not been clearly seen. The N-methyl group is also necessary for activity, since the N-demethyl analog (**10**) showed no activity. Most importantly, the basic indole lactam skeleton, "indolactam V' (**11**), seems to be a greatly responsible for the activity. This is indicated by the fact that there is a total loss of activities in the 2-oxo derivatives (**12a, b, 13a** and **13b**), and (-)-indolactam V has a weaker but reasonable activity, suggesting that an indolactam can be considered as the minimum active element of the teleocidins. Endo's group has synthesized indolactam V as the fundamental unit for further structure-activity relationship studies (Scheme I).[14]

Scheme I



A nonstereospecific pathway was chosen because it provided four stereoisomers for biological testing and led to the determination of the absolute stereochemistry of the teleocidins.[15] For the latter purpose, intermediate **14** was converted to diastereomeric esters **14a** and **14b** which were separated by chromatography and were converted to the corresponding alcohols **15a** and **15b**, respectively. The alcohol **15a**, derived from **14a** which gives (-) indolactam V (**11a**) and the C-12 epimer **16**, is identical with the one converted from L-tryptophan. Thus, the configuration at C-9 of the natural product was determined to be *S*. (Scheme II) The configuration at C-12 was deduced as *S* from the relative stereochemistry of teleocidins B-2 (**6b**), which was determined by X-ray crystallography. The CD spectrum of synthetic (-)-indolactam V corresponded well to that of **6b**.

Scheme II



The biological activity of all four isomer were tested and only the 9*S*, 12*S* isomer showed significant activity, suggesting that the stereochemistry of the nine-membered lactam is one of the most important factors for activity.[16] Further structural modifications were carried out using (-)-indolactam V. The results from the structure-activity studies of these synthetic derivativesin. indicate that O-alkyl derivatives (**17a-c**) greatly depress the activities, whereas the effect of acyl substitutions (**18a-c**) are low (Figure 3). This is probably due to intracellular enzymatic cleavage of the acyl group to reform **11a**.[17] Substitution at C-7 of the indole ring enhanced the activity. Although long chain alkyl groups (**19a-d**) were preferred, acyl (**20a-d**) and even heteroatom substituents (**21a-c**) enhanced the activity, which was consistent with the results from the natural products.[18] Alkyl substituents on N-1 showed slightly enhanced (**22a, b**: prenyl, geranyl) or slightly suppressed (**22c-g**: methyl to octyl) activity, implying that the indole imino group does not strongly participate in specific binding.[19a,b] Acylation of C-2 or C-5 (**23**) markedly lowers the activity, whereas halogenation of the same position (**24**) reduces it only slightly. This can not be explained by steric or electronic effects alone.[18a] The acid treatment of **11a** gave the ten-membered lactone **25** which showed no activity, again suggesting that the nine-membered lactam structure is indispensable.[13b]

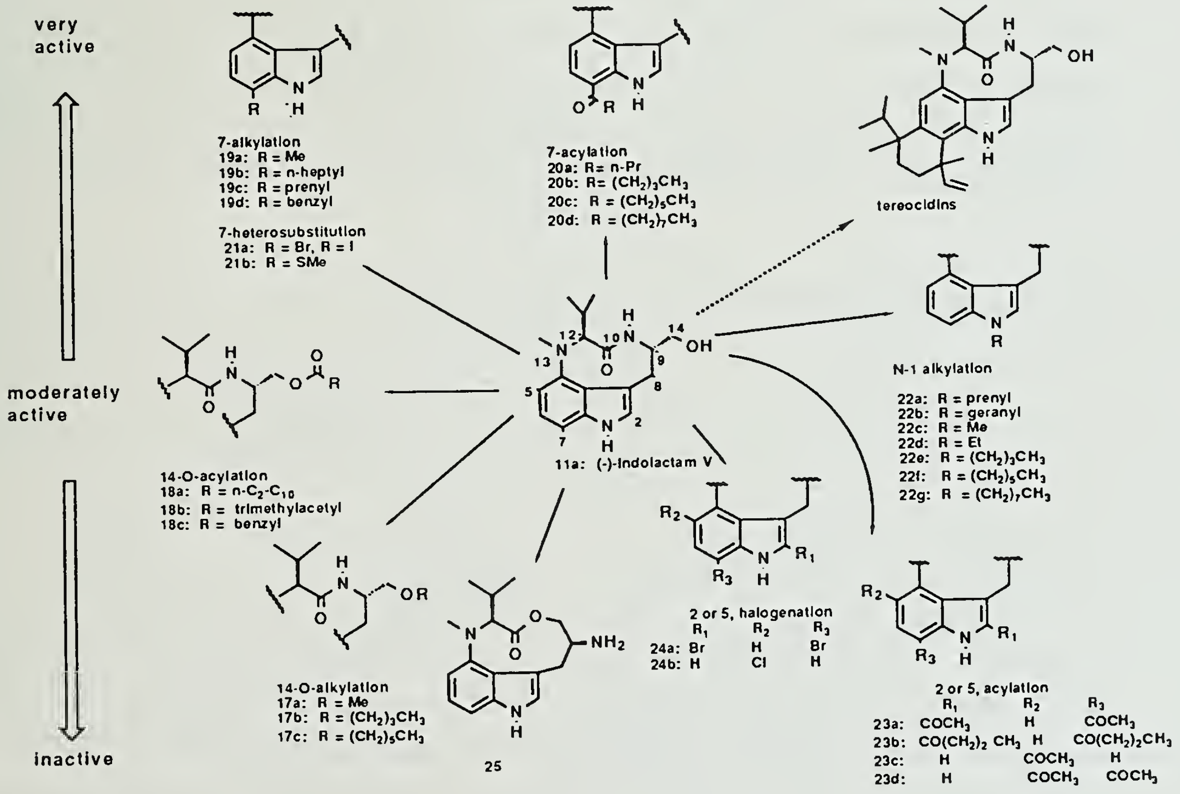
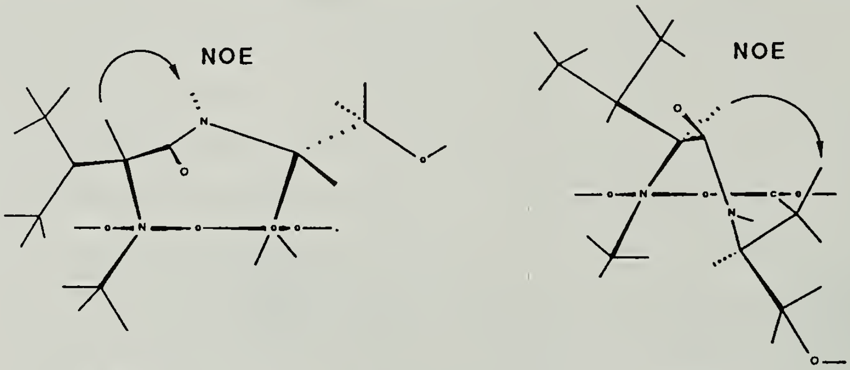


Figure 3

CONFORMATIONS OF INDOLACTAM

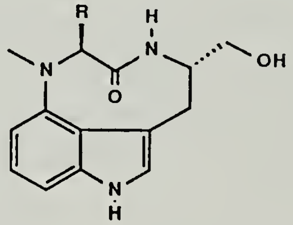
In solution, teleocidin and indolactams were always observed as mixture of two stable conformers by NMR spectoroscopy, even though X-ray studies show only one conformer. Endo's group analyzed these two conformers using NMR spectroscopy and computer assisted molecular modeling. These most stable conformers are the TWIST and SOFA forms (Figure 4).[15]



SOFA conformer TWIST conformer

Figure 4

The energy difference between the TWIST and the SOFA conformers was calculated based on successive measurements of the ratio of the two conformers by ^1H NMR spectroscopy at different temperatures. The results give an energy of activation, $\Delta G^{\#}$, of 18 kcal/mol and a half life of interconversion of 1.2 s at 37 °C, suggesting that both conformers must be taken into account when receptor models are studied.[14b, 15] Endo synthesized indolactam derivatives locked into one conformer or where a preponderance of one conformer exists in solution (Figure 5).



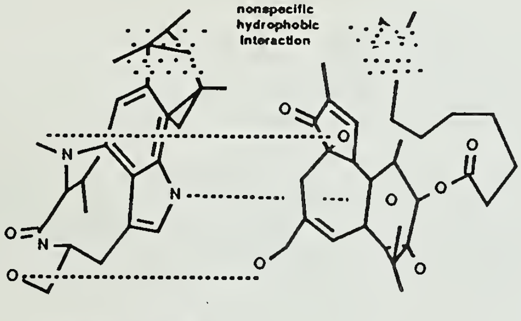
26: R = t-butyl
27: R = isobutyl
28: R = H
29: R = Me
30: R = $CH_2C_6H_5$

Figure 5

^1H NMR spectral studies of these C-12 modified derivatives showed that the TWIST and SOFA ratio in indolactams TL (**26**) and L (**27**) is 35:1 and 1:1 respectively, while the less bulky analogs indolactam G (**28**), A (**29**), and F (**30**) showed signals only for the TWIST conformer. Biological activity tended to increase when a larger substituent is attached to C-12. It is plausible from this result that the SOFA conformer has greater importance.[20, 21] From the results of both diterpene esters and teleocidins structure-activity studies, it appears that nonspecific lipophilic groups greatly enhance the activity, the free hydroxymethyl group plays an important role, and molecular shape/configuration is very important. And for the teleocidins, the SOFA conformer is reasonable to use for superposing the molecules.

MOLECULAR SUPERPOSITION OF TPA-TYPE TUMOR PROMOTERS.

Recently Jeffrey and Liskamp,[4a] Wender,[4b, c] and Endo and Sakai's[4d] groups have independently reported the computer assisted molecular modeling studies for TPA-type tumor promoters showing different results. Jeffrey's model, the earliest study, was constructed based on the incorrect stereoisomer of the teleocidin, which has later shown to be inactive.[4a] Wender's group used the correct isomer of the teleocidins and took into account most of structure-activity informations available and they superposed the molecules in terms of spatial positions of important heteroatoms and hydrophobic groups (Figure 6).

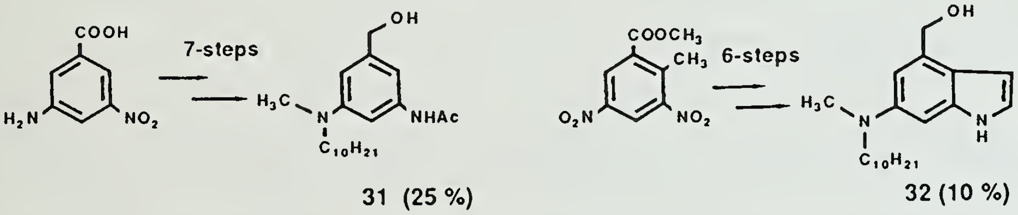


teleocidine B-4 TPA

Figure 6

Based on this result, Wender designed and synthesized model compounds **31** and **32** (Scheme III).

Scheme III



These molecule were superposed well on the TPA-type molecules and showed inhibition of [^{3}H]TPA binding and activation of protein kinase C in in vitro assays. On the other hand, Endo's group later developed a more precise model. They considered the spatial arrangement of functional groups in terms of their physical and chemical properties such as expected hydrogen bonding, electrostatic potential, charge distribution, and molecular occupancy instead of just surperposing the molecule, using teleocidin B-2 as the template molecule.[4d] This program allowed them to predict size, shape, and other nonbonding properties of the receptor cavity. Based on this model, Endo found that the SOFA form of teleocidin and TPA can have three common hydrogen bonding sites, whereas the TWIST form of teleocidin share only two.

CONCLUSION

Wender and Endo's molecular modeling studies provided common structual features of different classes of compounds, the diterpene esters and teleocidins, but their independent conclusions were different. Wender's group succeeded in designing "tumor promoters" using their model, suggesting that the model indicated some common receptor feature. Endo's model, on the other hand, took into account the conformational features of teleocidin and used more precise parameters to construct the model. Both models seem to explain most of the results from structure-activity studies, but they seem to be able to be improved by the further detailed studies. For example, instead of using X-ray structures of the diterpene esters to construct the models, it is important to use models of which the major conformation in solution is known. Also, some more structure-activity studies are necessary since compounds which are structurally very similar and appear to fit their model show no activitiy. Finally, designing and synthesizing potentially active molecules using Endo's model will provide further structure-activity informations.

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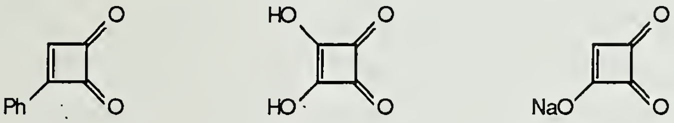
CYCLOBUTENEDIONES: VERSATILE PRECURSORS TO HIGHLY SUBSTITUTED QUINONES AND ALKYLIDENE CYCLOPENTENEDIONES

Reported by Monica J. Kochanny March 13, 1989

INTRODUCTION

Cyclobutenediones have been known since the 1950s, when Smutney and Roberts[1] and Cohen, et. al.[2] reported the syntheses of 3-phenylcyclobut-3-ene-1,2-dione **1** and 3,4-dihydroxycyclobut-3-ene-1,2-dione (squaric acid) **2**, respectively (Figure 1). The cyclobutenedione structure is also found in nature; the mycotoxin moniliformin,[3] isolated from *Fusarium moniliforme*, has been identified as the sodium salt of 3-hydroxycyclobut-3-ene-1,2-dione **3**.[4] Since the original syntheses, this class of compounds -- which can be formally considered to be quinones of the highly unstable cyclobutadiene -- has attracted considerable theoretical and synthetic interest.[5] Recently, synthetic routes have been developed for the regioselective formation of substituted benzoquinones and alkylidene cyclopentenediones from cyclobutenediones. Due to the potential use of these compounds in natural product synthesis, their syntheses will be discussed here.



1 2 3

Figure 1

CYCLOBUTENEDIONE SYNTHESIS

Early synthetic routes to substituted cyclobutenediones generally employed [2+2] cycloadditions of variously substituted alkenes and alkynes.[5a] These syntheses, however, were often characterized by severe reaction conditions and low yields. In addition, the nature of substituents which could be incorporated into the product was limited. In 1988, Moore[6] and Liebeskind[7] independently reported a method for the synthesis of cyclobutenediones possessing a wide variety of alkyl and aryl substituents. This method was based on earlier reports of the addition of Grignard and organolithium reagents to dialkoxycyclobutenediones (esters of squaric acid).[8] As shown in Scheme I, addition of an organolithium reagent to the dialkoxycyclobutenedione **4** occurred in a 1,2-fashion to give the 4-substituted-4-hydroxy-2,3-dialkoxycyclobutenone **5**. Hydrolysis to the cyclobutenedione **6** was effected either with

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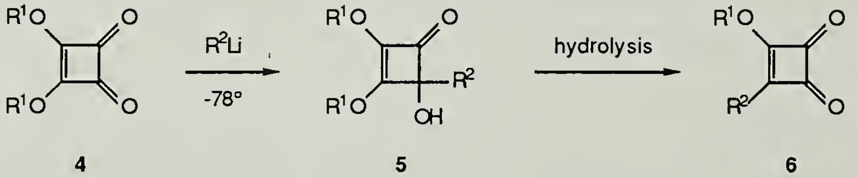
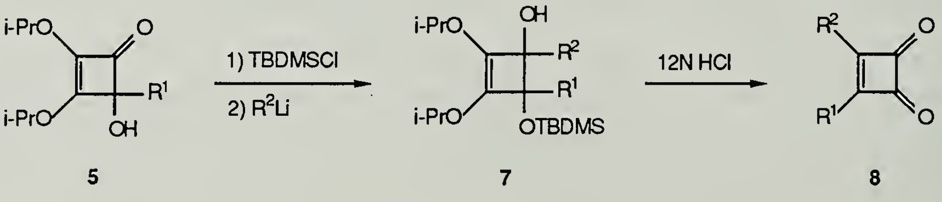
trifluoroacetic anhydride and pyridine[6] or by treatment of a methylene chloride solution of the alcohol **5** with 12N HCl.[7]

Scheme I



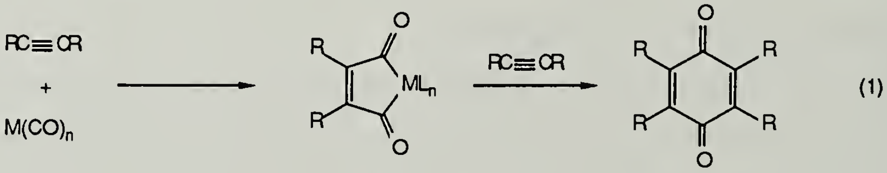
Liebeskind extended this method to the synthesis of dialkyl- (or aryl-) substituted cyclobutenediones (Scheme II). Protection of alcohol **5** (R^1 = i-Pr) as the tert-butyldimethylsilyl ether, followed by reaction with an organolithium reagent gave the adduct **7**. Subsequent hydrolysis led directly to the differentially disubstituted cyclobutenedione **8** in high yield.

Scheme II



QUINONE SYNTHESIS FROM MALEOYLCOBALT COMPLEXES

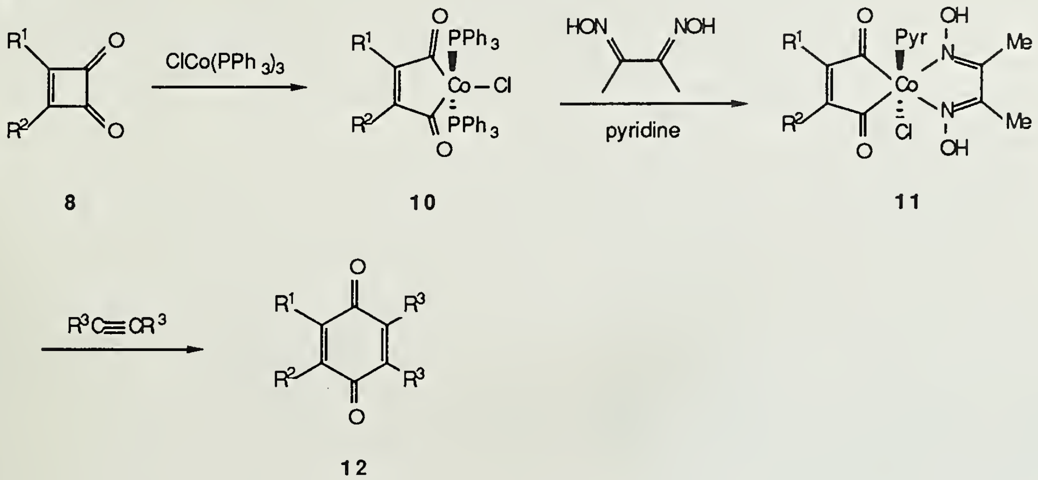
The formation of benzoquinones or benzoquinone-metal complexes by reaction of alkynes with stoichiometric amounts of transition metal carbonyl reagents is well-established.[9] This reaction has been suggested to proceed through an intermediate maleoylmetal complex **9** (equation 1).[9c,10] Liebeskind realized that the ability of low valent transition metal complexes to



9

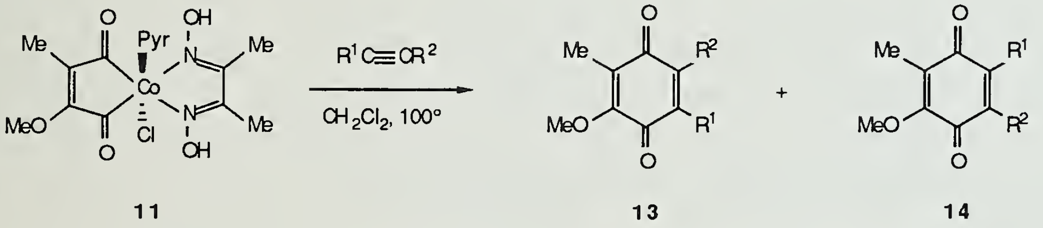
cleave small ring organic compounds[11] might allow the formation of complex **9** from cyclobutenediones, thus establishing a possible route to highly substituted benzoquinones.[12] This assumption was found to be correct, as cyclobutenediones reacted with $ClCo(PPh_3)_3$ to give the stable maleoylcobalt complex **10** (Scheme III). Complex **10** was treated with dimethylglyoxime in pyridine to afford the 6-coordinate, 18 electron complex **11**. Reaction of **11** with alkynes took place at 80°C to provide benzoquinones **12** in high yield. The regioselectivity of this reaction was studied by preparation of complex **11** (R^1 = Me; R^2 = MeO) from 3-methoxy-4-methylcyclobut-3-ene-1,2-dione. As shown in Scheme IV, reaction occurred with a variety of alkynes to give the benzoquinone **13** as the major isomer with moderate regioselectivity.

Scheme III



Further investigation revealed that upon addition of a stoichiometric amount of the Lewis acids $SnCl_4$, $BF_3{\cdot}Et_2O$ or $AgBF_4$, the reaction of **11** with three classes of alkynes (terminal, electron deficient, and propargylsilanes) proceeded at room temperature to give moderate yields of benzoquinones.[13] The regioselectivity under these conditions was much higher (7:1 to 20:1), with **13** again being the preferred isomer. Replacement of the Cl ligand of **11** with trifluoroacetate led to higher product yields.

Scheme IV

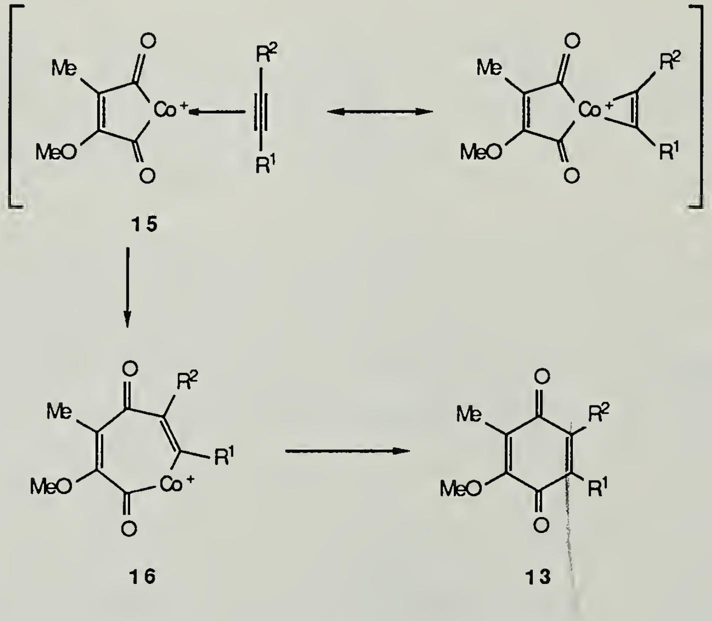


13a,14a	$R^1 = H$, $R^2 = t\text{-Bu}$	2.8:1
13b,14b	$R^1 = CO_2Et$, $R^2 = Me$	3.7:1
13c,14c	$R^1 = Me$, $R^2 = OEt$	13.5:1

Liebeskind has rationalized the regioselectivity of the thermal and Lewis acid-catalyzed reactions based on an alkyne insertion-reductive elimination pathway as shown in Scheme V. Upon chloride ligand ionization, the alkyne coordinates to give the cationic maleoylcobalt complex **15**. Insertion occurs by preferential migration of the less electron deficient acyl group onto the alkyne carbon which is best able to support positive charge, giving intermediate **16**.

Reductive elimination of cobalt then occurs to give the benzoquinone product **13**. This polarization model is consistent with the regiochemical outcome for each class of alkyne studied.

Scheme V

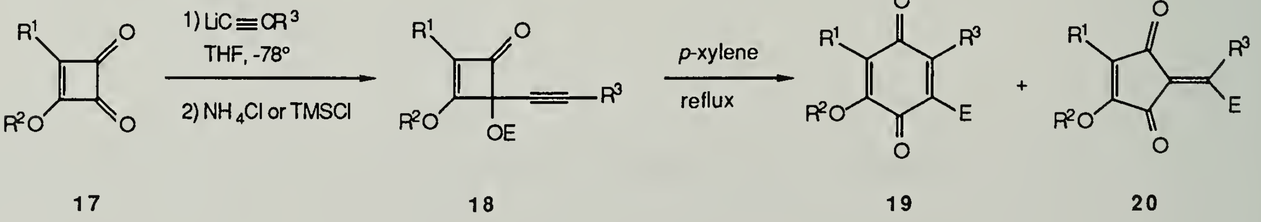


THERMAL RING EXPANSION OF 4-SUBSTITUTED-CYCLOBUTENONES

4-Alkynyl-4-hydroxycyclobutenones

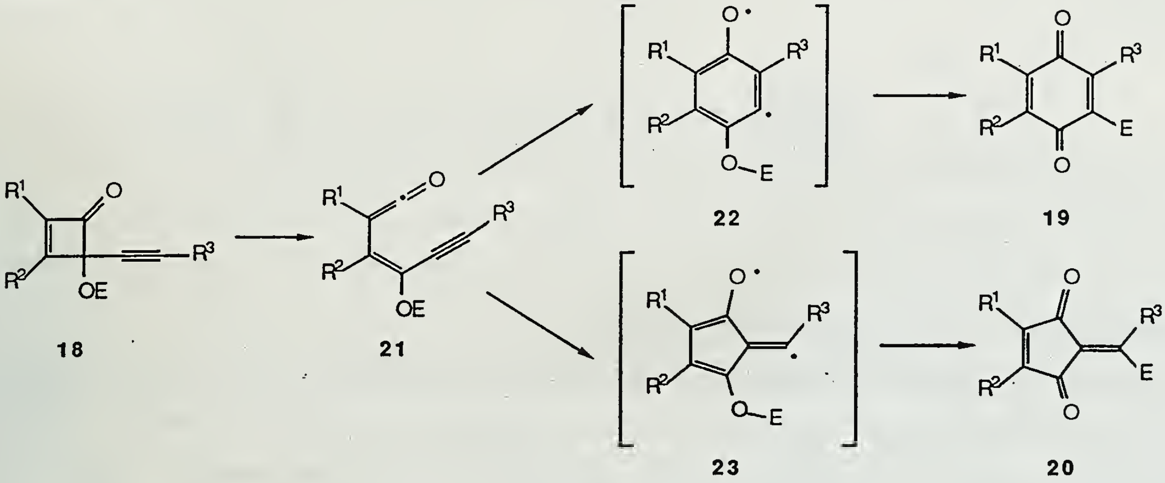
Moore has developed a synthetic route to benzoquinones via the thermal ring expansion of 4-alkynyl-4-hydroxy (or trialkylsilyloxy) cyclobutene-1-ones **18**.[14] As shown in Scheme VI, regioselective alkynylation of cyclobutenedione **17** (R^1 = alkyl, alkoxy), followed by protonation or silylation gives the alkynyl cyclobutenone **18**. Upon thermolysis in refluxing *p*-xylene, **18** undergoes ring expansion with transfer of the proton or trialkylsilyl group to yield the benzoquinone **19**. The reaction gives moderate to good yields of quinones when R^3 = alkyl. However, alkynes having $R^3 = C_6H_5$, OC_2H_5, or $CO_2C_2H_5$ resulted in partial to complete formation of the 2-alkylidene-1,3-cyclopentenediones **20**.

Scheme VI



The mechanism proposed for formation of **19** and **20** is shown in Scheme VII. Electrocyclic ring opening of **18** gives the (2-alkynylethenyl)ketene **21**. Ring closure of the ketene then occurs to give the diradical (or zwitterionic) intermediates **22** and **23** which, upon transfer of the substituent E, give the observed products. This mechanism requires a selective conrotatory electrocyclic ring opening of **18** such that the hydroxy or silyloxy group rotates outward, thus placing the alkyne in proximity with the ketene. This is supported by experimental[15] and computational[16] studies on the electrocyclic ring opening of cyclobutenes, which have indicated a strong preference for the outward rotation of electron donating substituents.

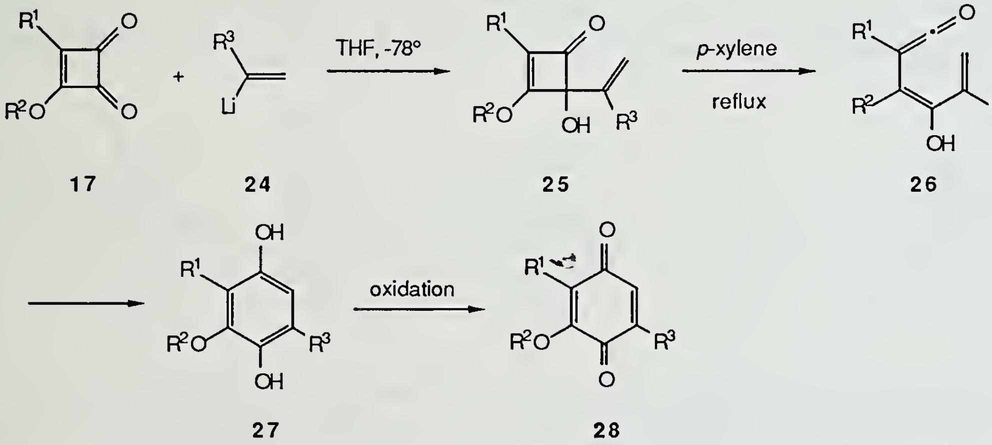
Scheme VII



4-Alkenyl-4-hydroxycyclobutenones

Moore has recently developed a synthetic route to 2,5-dialkyl-3-alkoxybenzoquinones **28**, the regioisomers of **19** (E = H).[17] As shown in Scheme VIII, vinyllithium reagents[18] **24** add to 3-alkoxy-4-alkylcyclobutenediones to give 4-alkenyl-4-hydroxycyclobutenones **25**. Thermolysis

Scheme VIII

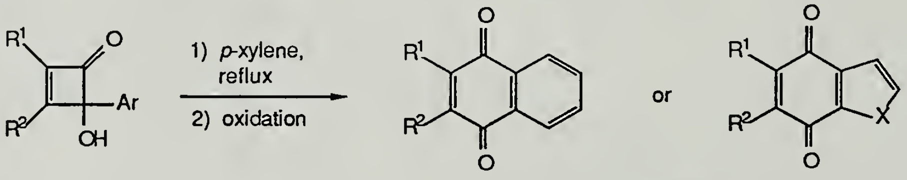


of **25** gives the hydroquinone **27**, presumably by electrocyclic ring closure of the intermediate ketene **26**. The hydroquinone is converted to the corresponding quinone **28** by an oxidative workup.

4-Aryl-4-hydroxycyclobutenones

The thermal rearrangement of 4-substituted-4-hydroxycyclobutenones was shown by Moore[14c,19] and Liebeskind[20] to extend to the 4-aryl- and 4-heteroaryl-substituted compounds. This route provides a regioselective synthesis of annulated benzoquinones. As with the alkenylcyclobutenones, thermolysis of **29** initially produces the hydroquinones. Oxidation with Ce(IV)/SiO_2 or Ag_2O gives the annulated quinones **30** or **31** (Scheme IX).

Scheme IX

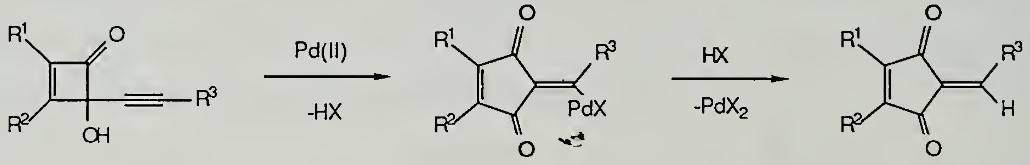


29 **30** **31**

ALKYLIDENE CYCLOPENTENEDIONES

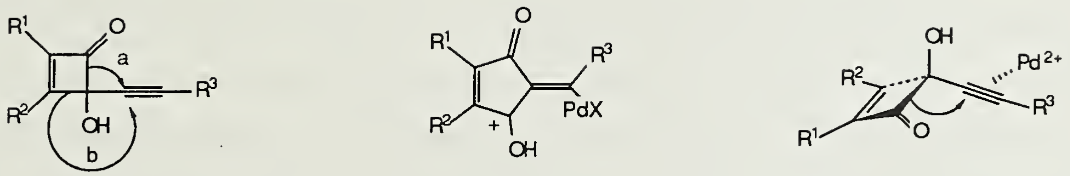
Liebeskind has recently developed a synthetic route to 2-alkylidene-1,3-cyclopentenediones, which are of interest as possible precursors for the synthesis of marine eicosanoid natural products.[21] Based on studies by Clark of 1-hydroxy-1-vinylcyclobutanes,[22] Liebeskind anticipated that reaction of 4-alkynyl-4-hydroxycyclobutenones **18** with an electrophilic palladium catalyst might result in ring expansion to alkylidene cyclopentenediones containing a vinyl-palladium bond **32** (Scheme X). Compound **32** could then undergo protonation by HX to form the alkylidene cyclopentenedione **33**, with regeneration of the palladium catalyst. This was shown to be the case: reaction of 4-(1-hexynyl)-4-hydroxy-3-methoxy-2-methylcyclobutenone (**18**, R^1 = Me, R^2 = OMe, R^3 = n-C_4H_9) with 10 mol % $Pd(OCOCF_3)_2$ produced the corresponding alkylidene cyclopentenedione in 45% yield as a 12:1 ratio of E:Z stereoisomers.

Scheme X



18 **32** **33**

The stereoselectivity of this reaction is dependent on two factors. First, there are two possible bonds, a or b, in **18** which could migrate to the adjacent alkyne carbon (Figure 2). The fact that only bond a migrates can be rationalized as being due to formation of the more stable cationic intermediate **34**. The selective formation of the E double bond isomer, then, is due to trans addition across the triple bond (**35**).



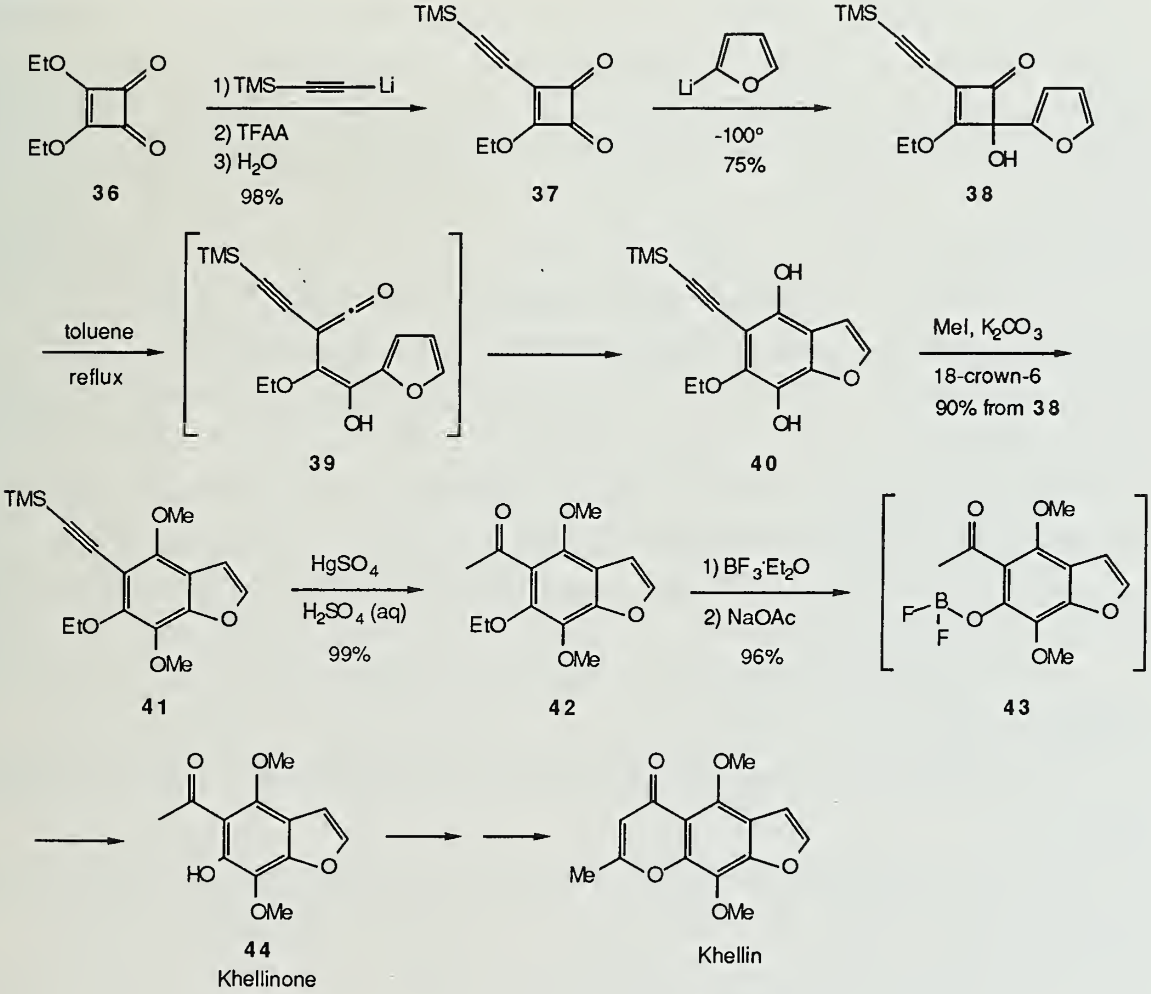
18 **34** **35**

Figure 2

APPLICATION TO NATURAL PRODUCT SYNTHESIS

Moore[23] has illustrated the applicability of cyclobutenediones to natural product synthesis in a formal total synthesis of the furochromone khellin (Scheme XI).[24] The major synthetic challenge in khellin synthesis is the construction of the aromatic B ring, which possesses four oxygen-containing substituents. Moore was able to differentiate among these substituents using the thermal ring expansion of 4-heteroarylcyclobutenones to 1,4-hydroquinones.

Scheme XI



The aim of Moore's synthesis was khellinone **44**, which has previously been converted to khellin in 85% yield.[25] The first key step involved the regioselective addition of 2-lithiofuran to the more electron deficient carbonyl of **37** to yield 3-ethoxy-4-(2-furanyl)-4-hydroxy-2-[2-(trimethylsilyl)-1-ethynyl]-cyclobut-2-ene-1-one **38**. Ring expansion in refluxing toluene, followed by methylation in situ produced the benzofuran **41**, which has the required four oxygen substituents in place. Mercury(II)-catalyzed hydrolysis of **41**, followed by selective cleavage of the ethoxy protecting group with BF_3 etherate,[25,26] completes the synthesis of khellinone. The overall yield of khellinone was 62% for six steps. This is a marked improvement over the previously most efficient synthesis, which gave khellinone in only 17% yield. Using an approach similar to that in Scheme XII, Moore has also synthesized the related furocoumarins pimpinellin and isophellopterin.[23a]

SUMMARY

Cyclobutenediones have been shown to produce highly functionalized benzoquinones and alkylidene cyclopentenediones in a highly convergent fashion. The high yield and regioselectivity of these reactions renders them useful as synthetic tools. Application to natural product synthesis has been demonstrated. It is expected that the above methods will lead to efficient syntheses of the quinone and cyclopentenone based natural products.

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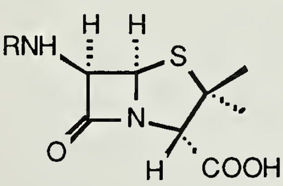
BIOSYNTHESIS OF NOCARDICIN A AND OTHER MONOCYCLIC β-LACTAMS

Reported by Byoung Wook Choi

March 16, 1989

INTRODUCTION

For many years, the penicillins (**1**) and the cephalosporins (**2**) were the only known, naturally occurring β-lactam antibiotics. However, advances in technology over the last 20 years have led to the discovery of a variety of other types of β-lactam antibiotics. One group that has been extensively studied is the monocyclic β-lactams.[1] These, in general, are active against Gram-negative bacteria, but show poor activity against Gram-positive bacteria.



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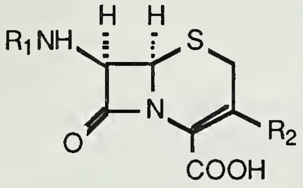
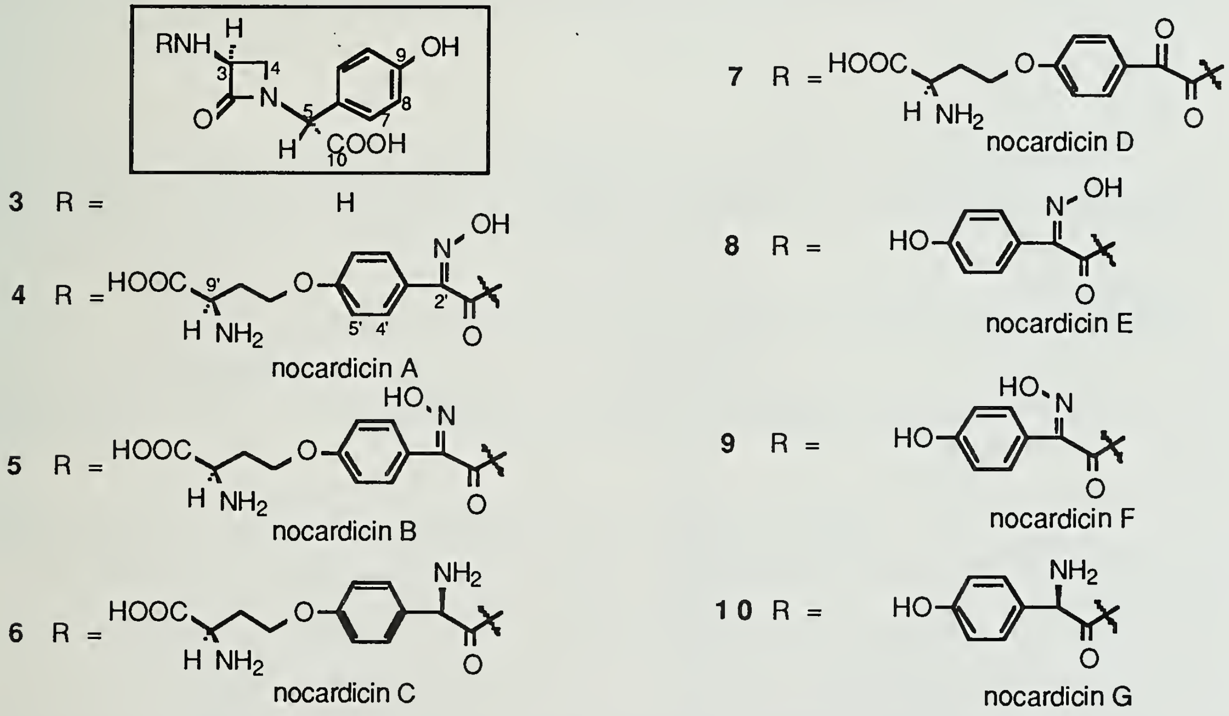


2

Nocardicins A-G (**4-10**) were first isolated from *Nocardia uniformis* subsp. *tsuyamanensis* in 1976.[2] More recently, the structurally related chlorocardicin[3] and formadicins[4] have been isolated from *Streptomyces* sp. and *Flexibacter alginoliquefaciens* sp., respectively.



A second class of monocyclic β-lactams is the monobactam,[5] which contains a sulfonic acid

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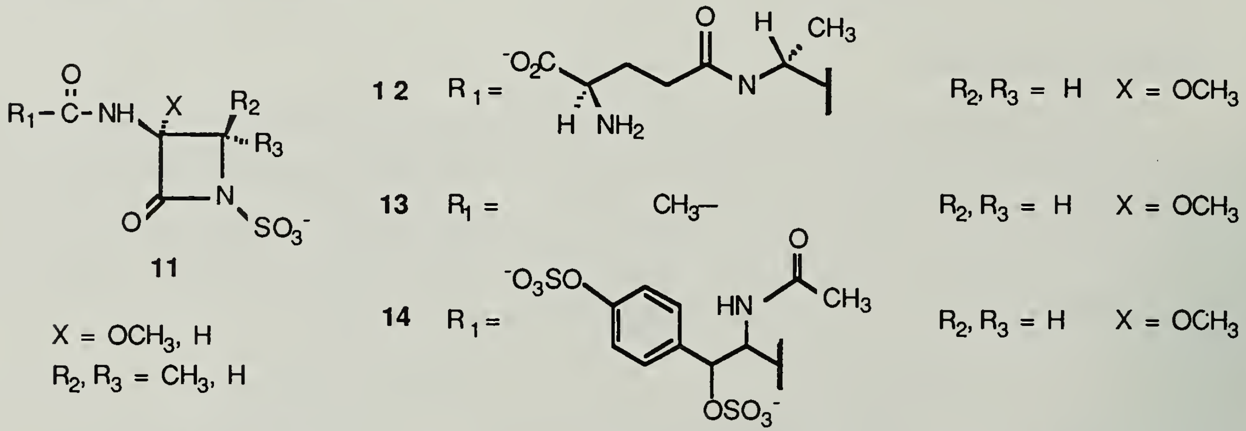
group on the β-lactam nitrogen (**11**). Among them, azetreonam[6] is now in clinical use and carumonam[7] is in clinical trials. Recently, some new synthetic monobactams involving different electronegative activating groups on the N-1 position, such as OSO_3^-, PO_3^-, OPO_3^-, OCH_2COO^- and tetrazole, have been reported.[3c]



Biosynthetic interest in the monocyclic β-lactams has led to the investigation of their biosynthesis. The origin of the β-lactam ring has been examined in several different compounds. Also, the unusual (*p*-hydroxyphenyl)glycyl and the ether-linked homoseryl units of nocardicin A have been studied. Sykes and co-workers have investigated the sources of the sulfur in sulfazecin (**12**), isolated from *Pseudomonas* and *Acetobacter* spp., SQ 26,180 (**13**), from *Chromobacterium violaceum*, and SQ 26,812 (**14**), from *Agrobacterium radiobacter*.[5b]

BIOSYNTHESIS OF NOCARDICIN A

Origin of the β-Lactam Ring

The origin of the carbon atoms in the β-lactam ring of **4** has been studied using ^{14}C and ^{3}H labeled amino acids (Table I).[8] Neither L-alanine nor L-cysteine are incorporated into nocardicin

Table I

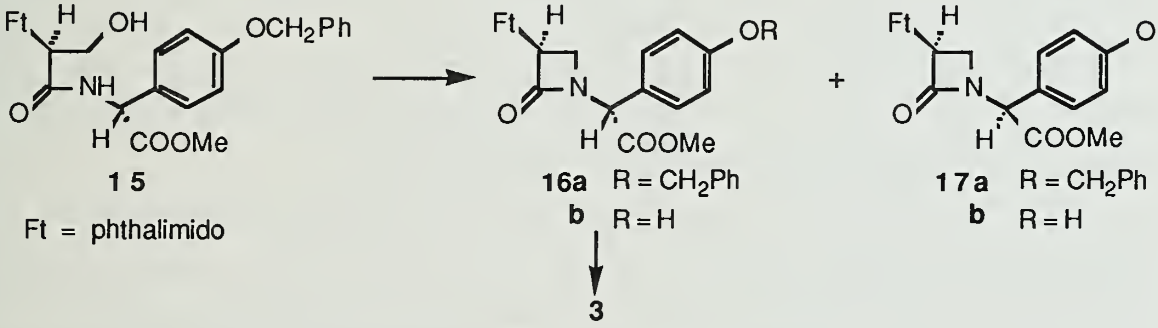
amino acid	^{14}C specific incorporation / unit	$^{3}H/^{14}C$ amino acid	$^{3}H/^{14}C$ **4**	% ^{3}H retained
L-[U-^{14}C]-Ala	0.07			
L-[U-^{14}C]-Cys	0.01			
[1-^{14}C]-Gly	2.6			
[2-^{14}C]-Gly	4.6			
L-[U-^{14}C]-Ser	7.8			
L-[3-^{3}H, U-^{14}C]-Ser	8.2	4.87	4.19	86
L-[3-^{3}H, 3-^{14}C]-Ser	5.8	3.74	3.70	99

A. The presence of cysteine reduces the production of **4** by about 90% compared to that in unsupplemented fermentation media. Glycine and L-serine, however, are both incorporated well into **4**. The higher incorporations of L-serine vs. glycine, and of [2-^{14}C]glycine vs. [1-^{14}C]glycine, suggests that L-serine is the actual precursor. It is known that [2-^{14}C]glycine labels the C-2 position of serine directly, and the C-3 position of serine is labeled indirectly via the C-1 pool and tetrahydrofolate.[9] This explanation is confirmed by feeding [2-^{13}C]glycine, which causes an enhancement of the resonances for C-3 and C-4 of **4** in a ratio of 3:2, while D,L-[3-^{13}C]serine enriches only the C-4 position of **4**.

Doubly labeled serine feeding experiments were used to determine the oxidation state during β-lactam ring formation. L-[3-^{3}H, U-^{14}C]serine and L-[3-^{3}H, 3-^{13}C]serine give 86% and 99% retention of tritium in **4** (Table I). These results suggest that the β-lactam ring is formed without a change in the oxidation state at the β-carbon. These results are in contrast to the oxidation state changes in penicillin[1c,10] and clavulanic acid[11] biosyntheses.

Incorporations of diastereotopically labeled [3-^{2}H]serines show that the stereochemical course of β-lactam ring formation is inversion,[12,13b] in contrast to that of penicillin.[1c] These results can be explained by a direct nucleophilic displacement of an activated seryl hydroxyl group by the amide nitrogen. To support this explanation (-)-3-aminonocardicinic acid (**3**) was synthesized (Scheme I).[13] Reaction of the optically pure serine-containing peptide (**15**) with triethyl phosphite and diethyl azodicarboxylate gave almost exclusively **16a** (diastreomeric purity of >50:1), which was hydrogenated and purified by crystallization to give optically pure **16b**. Compound **16b** was then deprotected to give **3**.

Scheme I



The Precursors of the Two Aromatic Amino Acid Segments

To probe the precursors of the aromatic amino acid segments, L-tyrosine (**18**), L-phenylalanine and D,L-(*p*-hydroxylphenyl)glycine (PHPG, **28**) were used for incorporation into nocardicin A (**4**) (Table II).[8] L-Tyrosine is well incorporated into **4** whereas L-phenylalanine is not. Experiments using L-[1-^{14}C]tyrosine as a precursor show that C-1 is lost, suggesting that the true precursor is PHPG (**19**). This is supported by the high incorporation (49.6%) of L-PHPG, and the specific incorporation of the C-1 carbon of D, L-[1-^{13}C]-PHPG into C-10 and C-1' of **4**. The lower incorporation of D-PHPG is precedented by the preference of L-valine in penicillin biosynthesis.[14] The complete loss of ^{3}H from D- and L-[2-^{3}H, 1-^{14}C]PHPG also corresponds to the fate of analogously labeled D, L-valine in penicillin biosynthesis.[15a]

Table II

	^{14}C specific	^{3}H / ^{14}C		
amino acid	incorporation / unit	amino acid	4	% ^{3}H retained
L-[U-^{14}C]-Tyr	15.0			
L-[1-^{14}C]-Tyr	0.03			
L-[U-^{14}C]-Phe	0.02			
L-[2-^{3}H, 1-^{14}C]-PHPG	49.6	4.44	0.06	1.3
D-[2-^{3}H, 1-^{14}C]-PHPG	6.3	4.45	0.04	0.9

The ^{1}H and ^{13}C NMR spectra of **4** produced by feeding D,L-[2-^{13}C, ^{15}N]-PHPG show that the β-lactam and oxime nitrogens originate from **PHPG**.[16] This result is consistent with the presence of ^{15}N in the incorporation studies of L-[2-^{13}C, ^{15}N]valine into penicillin.[15b,15c] Therefore, the oxime group in **4** is generated by stepwise oxidation of an amine-containing precursor rather than by the reaction of a keto intermediate with a hydroxylamine donor. Also, the equal extent of transamination in both nitrogen sites of **4** suggests a precursor containing two PHPG units.

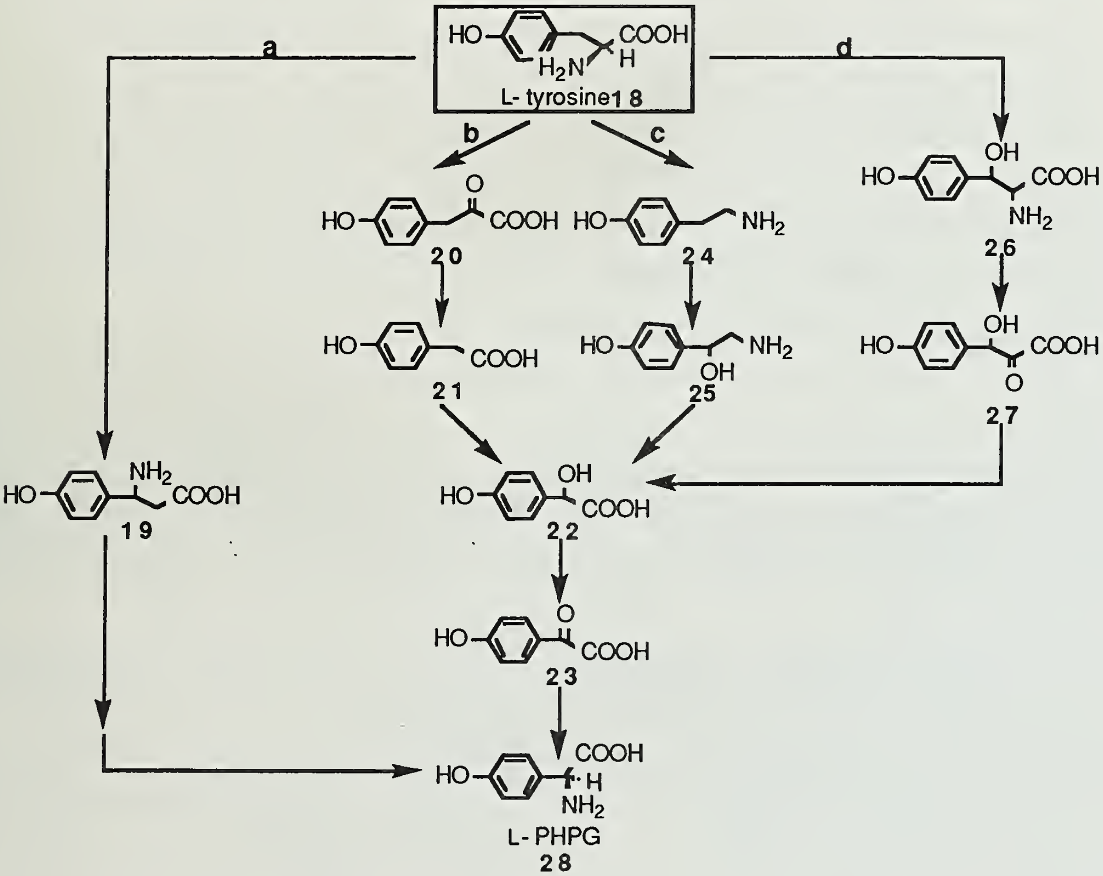
PHPG (**28**) is rarely encountered in natural products. This unit has been found only in the structurally similar group of antibiotics, which includes the vancomycins,[17] ristocetin A,[18] and avoparcin.[19] Interestingly, this group of compounds also contains (2S, 3R)- and (2R, 3R)-3-hydroxytyrosine (**26**) units. In addition, one of the recently found monobactams also contains a 3-hydroxytyrosine unit.[5b] The possible biosynthetic pathways of L-PHPG (**28**) from L-tyrosine (**18**) have been examined and are shown in Scheme II.[8a, 20, 21]

Incorporation of D, L-[2-^{13}C]tyrosine enriches the expected methine carbons of the 3-hydroxytyrosine unit and most of the carboxy carbons of the PHPG units of avoparcin.[19a] In addition, **26** and *p*-hydroxymandelic acid (**27**) have been incorporated into nocardicin A, whereas tyramine (**24**), octopamine (**25**) and *p*-hydroxyphenylacetic acid (**21**) have not. Therefore, at least tentatively, path d in Scheme II is the biosynthetic route to PHPG from tyrosine.

Formation of the Ether Linkage

Nocardicin A contains a homoseryl unit (C-7' - C-10') into which L-[U-^{14}C]homoserine shows a positive incorporation (1.5%). However L-[1-^{14}C]methionine shows much higher incorporation (19.6%).[8] This suggests that the ether bond is formed by direct S_N2 displacement of methionine via its activated form, S-adenosylmethionine (SAM),[22] or by a pyridoxal phosphate dependant γ-replacement reaction.[23] To probe these possibilities, (2S, 4R)- and (2S, 4S)-[4-^{2}H]methionine have been synthesized and used for feeding studies.[24] Both compounds are incorporated with inversion of configuration. These results correspond to the steric course of polyamine biosynthesis and suggest that the 3-amino-3-carboxylpropyl group is transferred by an S_N2 displacement on SAM.[22,25]

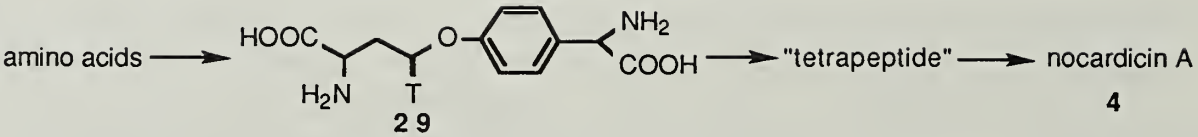
Scheme II



Biosynthetic Pathway to Nocardicin A

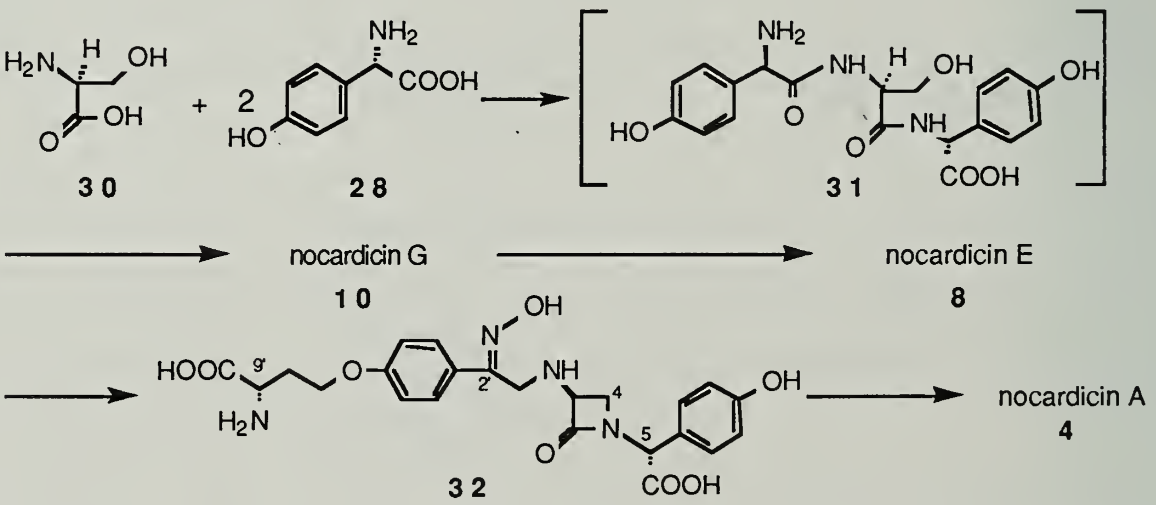
In addition to studying the primary metabolites which are precursors to **4**, Townsend and co-workers have investigated the sequence in which they are assembled.[26] The tritiated aryl-alkyl ethers (**29**) have been synthesized to determine when the homoseryl unit is incorporated during the biosynthesis of **4**. The absence of radioactivity in **4** produced by feeding **29** excludes the possibile biosynthetic pathway shown in Scheme III,[27] and implies that ether formation is a late step in the pathway.

Scheme III



Nocardicins E, F and G (**8**-**10**), minor metabolates of the nocardicin family, do not contain homoserine units, which indicates that the homoserine unit is not necessary for β-lactam ring formation. The intact incorporation of [2'-^{13}C, ^{15}N]nocardicin G (**10**) into **4** has also been demonstrated.[27] However, the incorporation of [2'-^{13}C, ^{15}N]epinocardicin G, the 2'-epimer of **10**, shows randomization of the carbon label into C-5 and C-2' of **4** and a loss of 25-30% of ^{15}N due to degradation of **10** to PHPG prior to utilization. Also, cell-free extracts of *N. uniformis* produce a mixture of [2'-^{13}C]nocardicin A and its C-9' epimer when [2'-^{13}C]nocardicin E (**8**) is incubated with SAM. These results, therefore, strongly suggest the general biosynthetic route to nocardicin A (Scheme IV). L-Serine (**30**) and PHPG (**28**) are combined first to give L- or D-PHPG-L-Ser-D-PHPG peptide (**31**). Ring closure of the tripeptide gives nocardicin G (**10**), which has a DLD-configuration. Amine oxidation at this center then yields the 2'-*syn*-oxime of nocardicin E (**8**). The homoserine unit is then attached to form isonocardicin A (**32**), which is epimerized at the C-9' position to give **4**. The epimerization of **32** to **4** is monitored in vitro by the disappearance of the H-9' resonance in the ^{1}H NMR when pure nocardicin A (**4**) is incubated in deuterium oxide with cell-free extracts.

Scheme IV



BIOSYNTHESIS OF OTHER MONOBACTAMS

β-Lactam Ring Formation

The biosynthesis of the monobactams **12**, **13** and **14** have also been studied,[28] but to a lesser extent. β-Lactam formation in these compounds is similar to that of **4**. L-Serine, L-glycine and pyruvate are all incorporated into **14** by *C. violaceum*, while, in contrast to nocardicin A, L-cysteine is also incorporated. Neither alanine nor aspartate serve as precursors. Again, the higher incorporation of [2-^{14}C]glycine vs. [1-^{14}C]glycine into **13** indicates that glycine is first converted into serine via tetrahydrofolate pathway.

Incorporation of a mixture of [U-^{14}C]serine and [3-^{3}H]serine into **12**, **13**, and **14** shows the complete retention of tritium. This suggests a direct S_N2 ring closure reaction as in **4** without oxidation of hydrogen at C-3. The results from a similar experiment with [U-^{14}C]cystine and [3-^{3}H]cystine in *C. violaceum* appears to contradict this theory, as extensive loss of tritium was observed. However, an alternative explanation for the cystine case is that cystine is modified before its incorporation into **14**. The cell-free extract of *Acetobacter* sp. and *C. violaceum* show desulfhydrase activity.[29] With [U-^{14}C]- and [3-^{3}H]cysteine as a substrate, these extracts give alanine as a major product. The ratio of ^{14}C to ^{3}H in the alanine produced shows more than 80% loss of tritium. Therefore, there is extensive exchange of ^{3}H at the C-3 of cysteine.

Origin of the Sulfamate Sulfur

The sulfur metabolism of *C. violaceum*, *Acetobacter* sp. and *A. radiobacter* has also been studied.[29] A variety of sulfur-containing compounds have been tested for their effects on monobactam production, as shown in Table III. These results indicate that these three organisms differ in their ability to utilize various sources of sulfur. While all of them can use inorganic sulfur, only *Acetobater* and *C. violaceum* can use organic sulfur sources. ^{35}S labeled cysteine,

Table III

Sulfur source (1mM)	Monobactam production (µg/mL) *A. radiobacter*	*Acetobacter* sp.	*C. violaceum*
none	-	-	-
Na_2SO_4	43	55	12
$MgSO_4$	48	55	14
cysteine	-	51	a
cystine	-	50	13
methionine	-	52	-

a: Growth was inhibited by cysteine.

sodium sulfate and methionine has been used to determine the source of sulfur in **12**. About 0.5% of ^{35}S is incorporated in all cases.

The reaction of [^{35}S]cysteine with cell-free *Acetobacter* extracts having desulfhydrase activity gives a $^{35}SO_4^{2-}$ product which has been analyzed by electrophoresis and fluorography. Incubation of cell-free *A. radiobacter* extracts with ATP and $^{35}SO_4^{2-}$ generates adenosine phosphosulfate (APS) as a major product and a slight amount of phosphoadenosine phosphosulfate, whereas under the same conditions cell-free extracts of*Acetobacter* and *C. violaceum* do not. This indicates that cell-free *A. radiobacter* extracts contain enzymes for the activation of sulfate. Since all three organisms have the ability to form sulfate from sulfur-containing amino acids and can utilize inorganic sulfate as a sulfur source, it is suspected that activation of sulfate is likely to procede before incorporation into the β-lactam ring.

CONCLUSION

The overall biosynthetic pathway to nocardicin A has been fairly well substantiated. Nocardicin A is totally amino acid-derived, like penicillin N and cephalosporin C. Nocardicin A originates from L-methionine, L-serine and L-(*p*-hydroxyphenyl)glycine, which in turn is derived from tyrosine. The β-lactam ring is formed via direct nucleophilic ring closure without a change in the oxidation state of C-3 serine. Sulfazecin, SQ 26,180 and SQ 26,812 also show the same pattern of ring closure as nocardicin A. The sulfamate sulfur of these monobactams is formed from activated inorganic sulfate.

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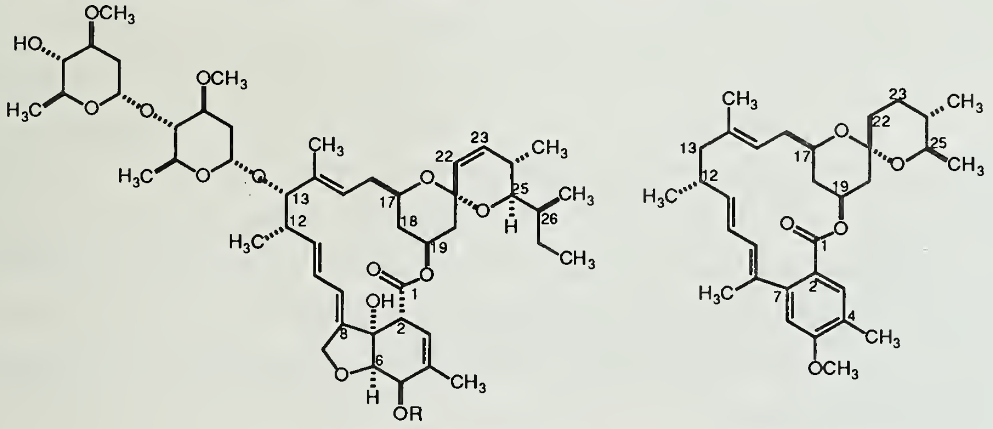
THE TOTAL SYNTHESIS OF AVERMECTINS AND MILBEMYCINS

Reported by Jung Ho Kim March 27, 1989

INTRODUCTION

Avermectins,[1] macrolide antibiotics exhibiting highly potent activities to nemetodes and arthropods, were isolated from *streptomyces* spp. after a screening effort by Merck in 1979. The structures were confirmed and stereochemistry determined by X-ray analysis of crystalline avermectin B2a aglycone and avermectin B1.[2] Structurally similar milbemycins, which also show insecticidal and acaricidal effects, were discovered by Japanese workers in a search for fermentation products with pesticidal activity.[3]

Both the avermectins and milbemycins are sixteen-membered lactones with a spiroketal system comprising two six-membered rings. The principal difference is that avermectins have an α-L-oleandrosyl-α-L-oleandrosyl disaccharide attached at the C13 position whereas the milbemycins do not. In addition, the avermectins differ in substituents at the C25 position, and also have a C22-C23 double bond, which is absent in the milbemycins (Figure 1).



1a $R=CH_3$ Avermectin A1a
b R=H Avermectin B1a

2 Milbemycin β3

Figure 1

Owing to the unique biological activities of milbemycins and avermectins as well as their challenging structural features, these compounds have been synthetic targets for the last decade. Several total syntheses of milbemycin β3,[4] two total syntheses of avermectin A1a and B1a,[5] and a variety of partial syntheses including model approaches to the spiroketal unit[6,7] and the hexahydrobenzofuran unit[8] have been reported.

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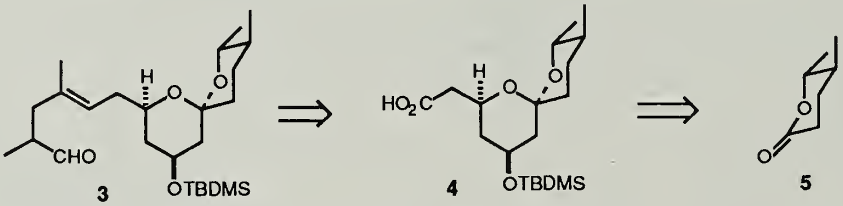
The general strategies for the syntheses of both milbemycins and avermectins start from three subunits; the spiroketal unit, the side linkage including C-13 sugar substituent, and hexahydrobenzofuran or substituted aromatic unit completes the formation of macrolactone. The key approaches in the syntheses of milbemycins and avermectins, including substructures, will be discussed here.

SYNTHETIC STUDIES

Synthesis of the Spiroketal Unit of Milbemycin β3

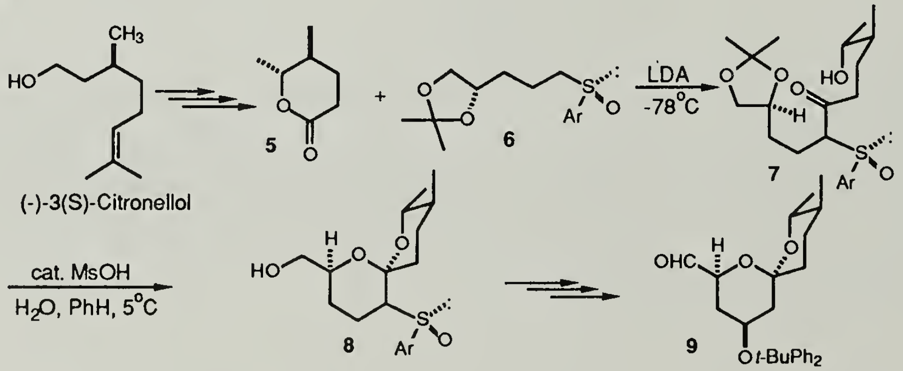
In the first synthesis of (±)-milbemycin β3, Smith[4a] initially divided milbemycin β3 into the spiroketal (**3**) and an aromatic part. The synthesis of the spiroketal unit started from the racemic lactone **5** and utilized the anomeric effect in forming the spiroketal under equilibrating conditions (Scheme I).[9] The spiroketal oxygens were placed at the axial positions with respect to the conspecific rings in order to maximize stabilizations due to the anomeric effect.

Scheme I



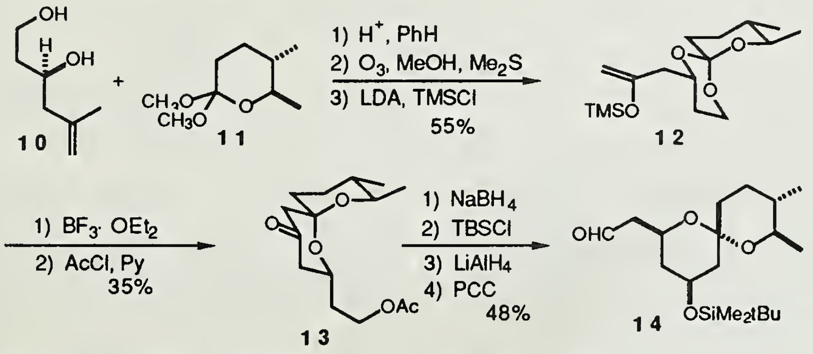
The first synthesis of enantiomerically enriched milbemycin β3 was accomplished by Williams.[4b] He used an optically active starting material, (-)-(3S)-citronellol to construct chiral lactone **5**. Subsequent condensation of **5** with the α-lithiosulfoxide **6** yielded a mixture of two diastereomers. The major product cyclized with a catalytic amount of acid exclusively to afford spiroketal **8**, owing to the anomeric effect. Spiroketal **8** was further converted to **9** after a few chemical reactions (Scheme II).[9]

Scheme II



A slightly different approach to the spiroketal synthesis was utilized by Kocienski.[4d] He used a Lewis acid catalyzed intramolecular directed aldol reaction of spiro orthoester intermediate **12** through the dioxonium ion intermediate to yield a spiroketal **13**. Subsequent reduction, protection, and side chain oxidation of **13** gave **14** (Scheme III).

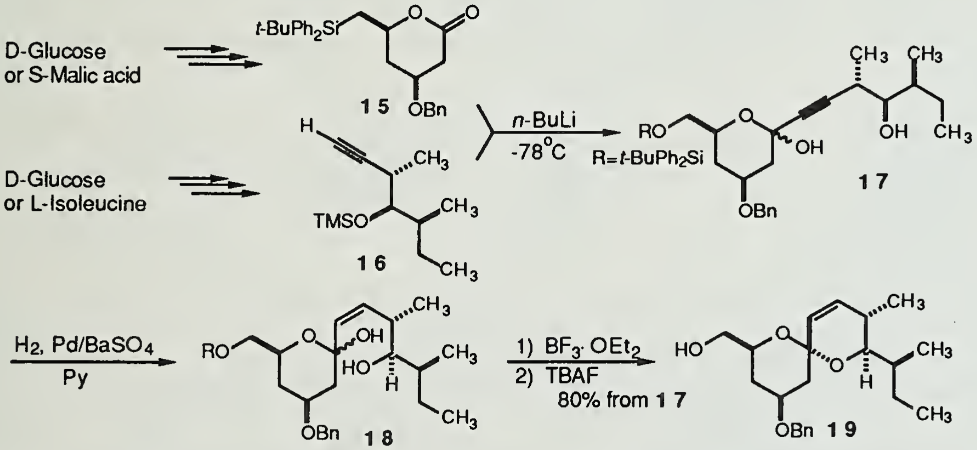
Scheme III



Synthesis of the Spiroketal Fragment of Avermectins

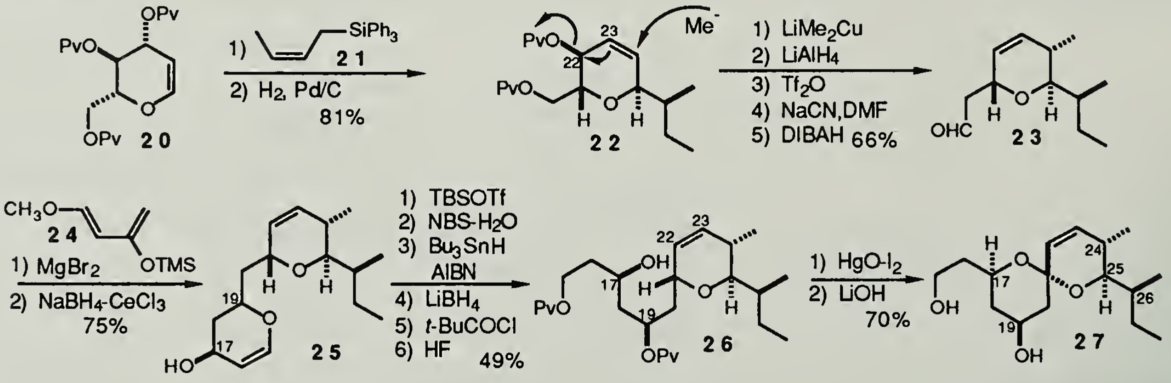
Hanessian[6a] reported the preparation of the spiroketal unit **19** based on the chiron approach[10] in the first total synthesis of avermectin B_{1a} aglycone.[5a] The spiroketal was formed through the condensation of lactone **15** and acetylene **16**, which were derived from D-glucose and (S)-malic acid by standard chemical reactions. Reduction to the *cis* olefin and eventual internal ketalization relying on anomeric stereoselection[9] gave the thermodynamically favored isomer as a single diastereomer **19** (Scheme IV).

Scheme IV



In the synthesis of avermectin A1a[5b], Danishefsky took advantage of his recently developed "carbon-Ferrier" technology.[11] The synthesis started with the D-glycal derivative **20**. Through the use of successive S_N2 displacements with the silane and the cuprate reaction, the chiral imprint of the glucal was conveyed to C24, C25, and C26 of the avermectin precursor and the double bond was installed between C22 and C23. He controlled the other stereogenic centers at C-19 and 17 by forming the pyrone-pyran system followed by regio- and stereo-controlled 1,2 reduction of the cyclic enone.[12] The major pyrone-pyran product (3.5~5.0:1), represented as **25**, is the product arising from the chelated conformer which undergoes cyclocondensation from the less hindered side. After several preliminary reactions, HgO-I_2[13] was used to form the spiroketal. This critical oxidative cyclization gave only one spiroketal due to anomeric effect (Scheme V).[9]

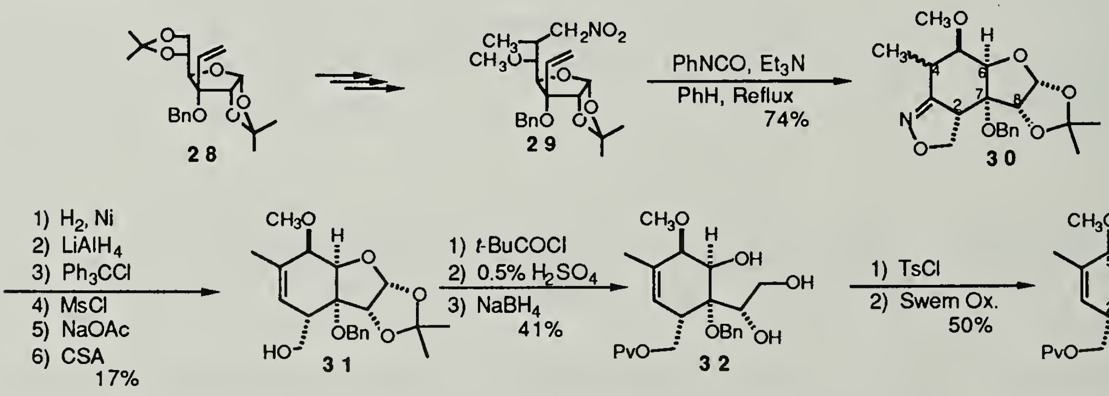
Scheme V



Synthesis of the Optically Active Hexahydrobenzofuran unit of Milbemycins and Avermectins.

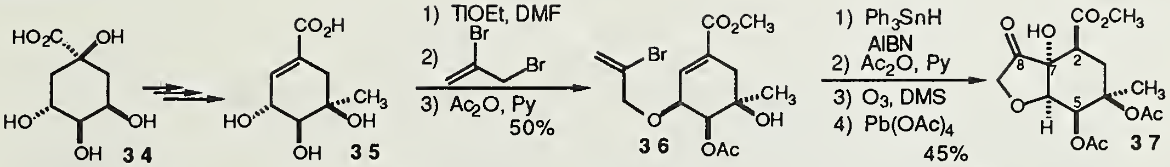
The hexahydrobenzofuran subunit has a tertiary hydroxyl group which is prone to elimination and aromatizatoin. There are relatively few reports[8] of the synthesis of the hexahydrobenzofuran unit. Fraser-Reid[8d] reported the first chiral synthesis of hexahydrobenzofuran **33** starting from diacetone glucose derivative **28**. The key step is an intramolecular nitrile oxide cycloaddition[15] to afford **30** as a single C2 diastereomer. Subsequent reduction and β-elimination also gave a single olefinic isomer **32**, which was ultimately converted to the hexahydrobenzofuran **33** (Scheme VI).

Scheme VI



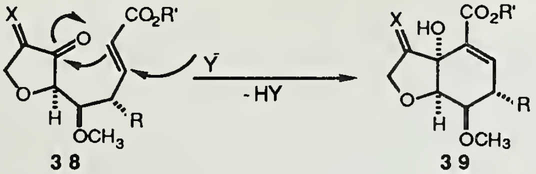
Hanessian's approach[8b] employed an optically active precursor, readily available (-)-quinic acid(**34**). His synthetic strategy relied on Michael type radical ring closure of **36** to form the hydrobenzofuran ring, followed by introduction of an angular hydroxy group to afford key intermediate **37** (Scheme VII).

Scheme VII

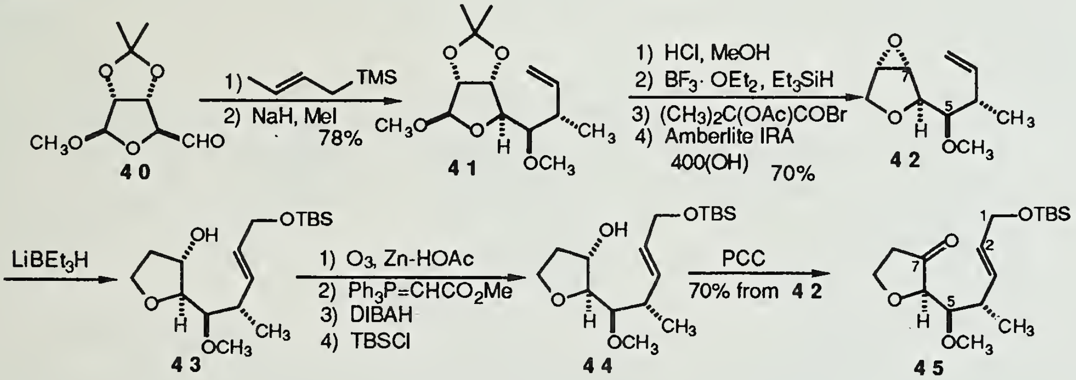


Danishefsky's approach to the synthesis of hexahydrobenzofuran unit is based on the synthesis of hexahydrobenzofuran precursor **38**, which can undergo an intramolecular Nozaki process (Scheme VIII)[17] after attachment of the side chain linkage and the spiroketal unit. The synthesis of **38** started with the D-ribose derived aldehyde **40**. After a few chemical transformations including an allyl silane aldol reaction, formation of the epoxide, and extention of the side chain by Wittig type olefination, he obtained an appropriately substituted 3-furanone derivative **45**, which can be further converted to **38** (Scheme IX).

Scheme VIII

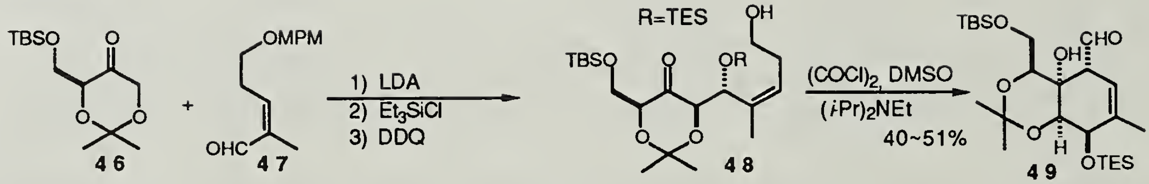


Scheme IX

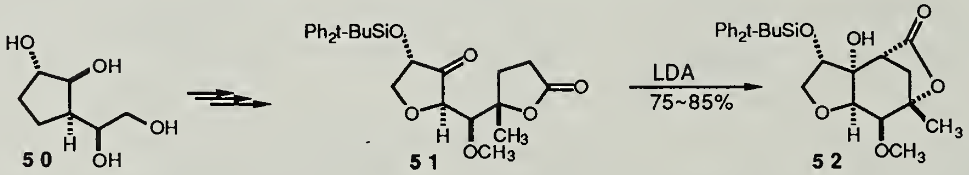


Recently, Hirama[8f] and Willams[8g] reported the synthesis of the hexahydrobenzofuran subunit. Hirama relied on two successive aldol reactions to assemble four stereogenic centers in the hexahydrobenzofuran unit (Scheme X). The first aldol condensation between **46** and **47** gave an 8.3:1 ratio of 5,6-antidiastereomers. The subsequent intramolecular aldol reaction of **48**, under *in situ* oxidation condition, generated two stereogenic centers at C2 and C7 with almost complete control (Scheme X). Willams chose the bicyclic lactone **52** as a subunit to prevent the formation of the C2 epimer and the isomerization of the C3-C4 double bond. Intramolecular Claisen condensation of **51** proceeded to afford a single *cis*-fused oxahydrindane **52** (Scheme XI).

Scheme X



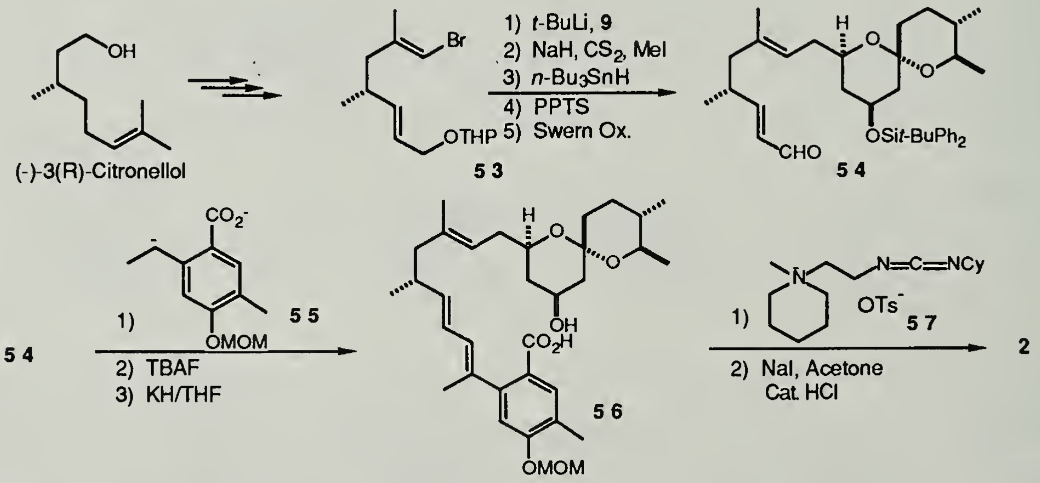
Scheme XI



Construction of the Side Linkage and Completion of the Total Synthesis of Milbemycin β3

While Smith completed the total synthesis of (±)milbemycin β3,[4a] Williams assembled spiroketal **9** with a side linkage **53**, which was prepared from (-)-3(R)-citronellol. After Barton's dehydroxylation, deprotection, and oxidation of allylic alcohol, the resulting spiroketal aldehyde **54** was coupled with substituted aromatic anion **55**. The total synthesis of (-)-milbemycin β3 (**2**) was completed after macrolactonization of **56** (Scheme XII).[4b]

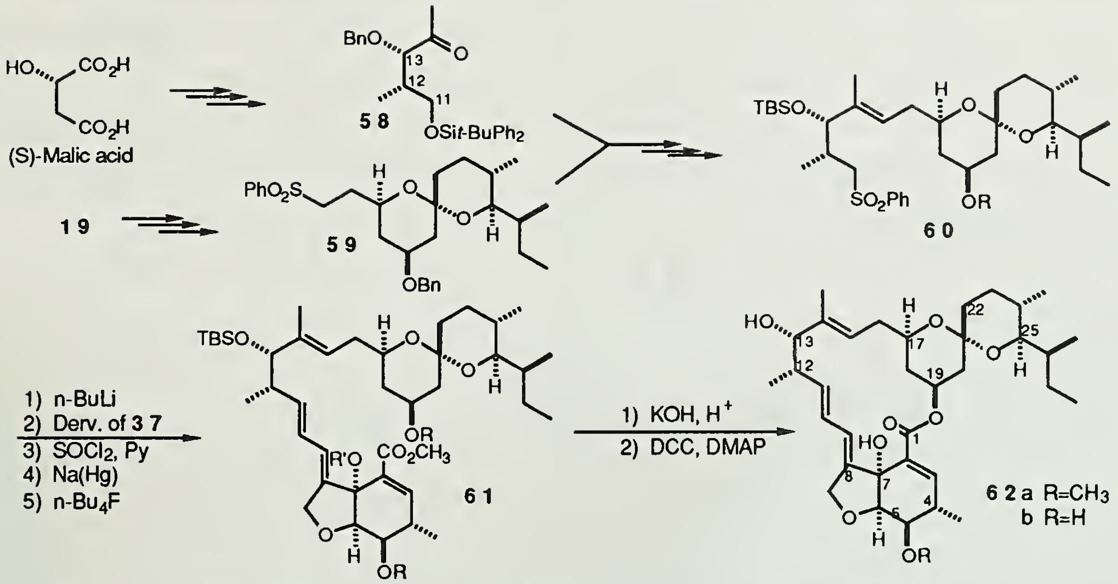
Scheme XII



Synthesis of Avermectin Aglycone

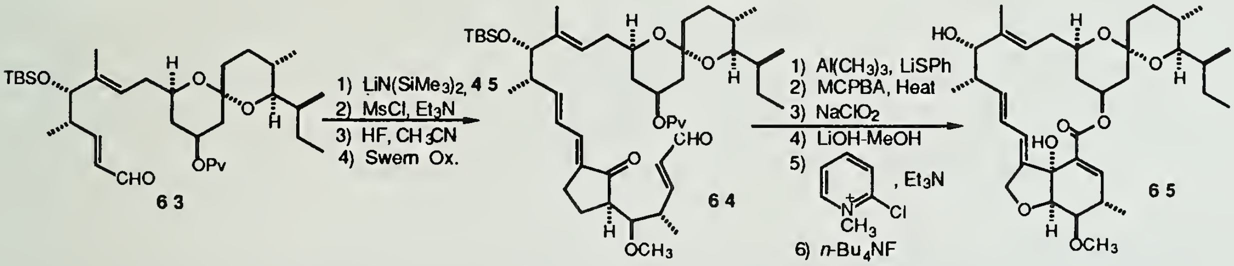
In the total synthesis of avermectin B1a, Hanessian[5a] assembled a C11-C14 segment derived from (S)-malic acid, with a spiroketal derived from **19** by the sulfone anion condensation. The resulting subunit **60** was coupled to the hexahydrobenzofuran unit which was initially prepared from the degradation of natural avermectin B1a and synthesized later from (-)-quinic acid. macrolactonization completed the synthesis of avermectin B1a aglycone (Scheme XIII).

Scheme XIII



After side chain installation utilizing the crotonyl boronate chemistry of Roush[18], Danishefsky excuted the intramolecular Nozaki process.[17] Intermolecular aldol condensation of **63** with **45** gave Nozaki precursor **64**. The synthesis of aglycon **65** was completed after double bond installation followed by macrolactonization (Scheme XIV).

Scheme XIV



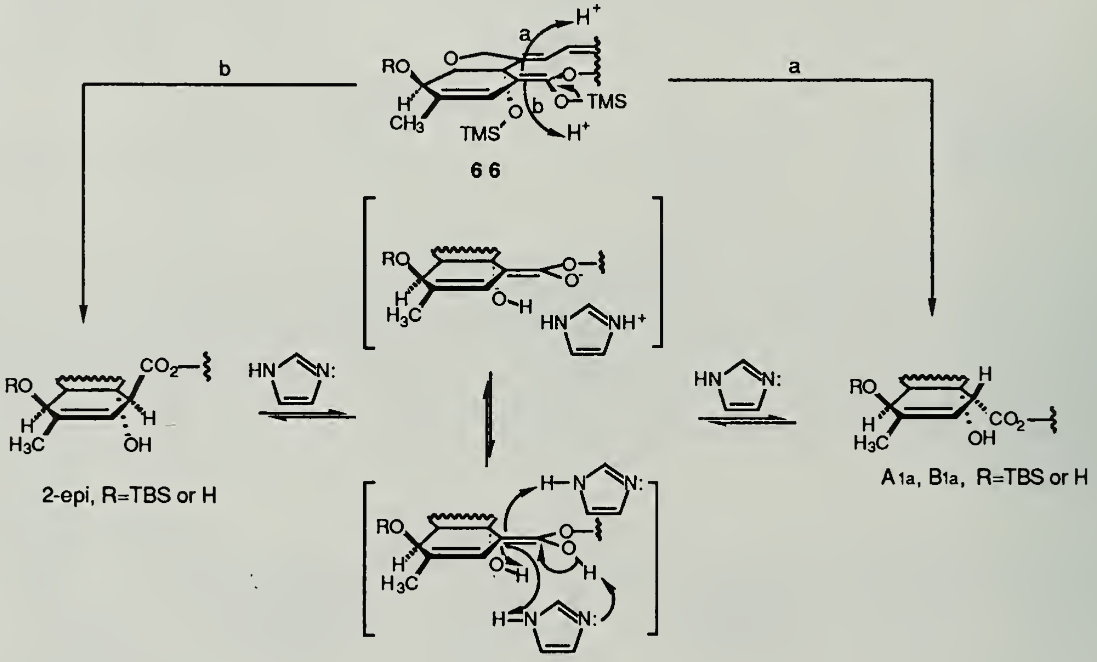
Glycosylation and Deconjugation: Completion of the Total Synthesis of Avermectin A1a and B1a

Hanessian glycosylated the C13 O-silylated derivative of **62b** with pyridylthioglycoside in the presence of silver triflate[19] and carried out deconjugation of conjugate C2-C3 double bond to complete the total synthesis of avermectin B1a. After the deconjugation of aglycone **65**, Danishefsky carried out a glycosylation using *N*-iodosuccinimide promoted etherification[20] to complete the total synthesis of avermectin A1a.

Each glycosylation gave predominantly the α-anomer. However, deconjugation, which was described as a "last hurdle" gave a variety of products depending on reaction conditions.[21]

Hanessian obtained the avermectin B1a in 72% yield based on recovered materials in the final deconjugation step after silylation of the C-7 hydroxy group, followed by formation of ketene acetal **66**, and subsequent careful acidification and desilylation (Scheme XV). Danishefsky benefitted from the revised Hanessian's epimerization methodology.[22] He used imidazol in refluxing benzene to afford a 32% of avermectin A1a aglycone with a 2-epi isomer and a conjugated isomer(Scheme XV).

Scheme XV



CONCLUSION

In summary, many different syntheses of milbemycin β3 and avermectin A1a and B1a have been achieved starting from chiral building blocks. Several approaches aimed at the synthesis of the spiroketal unit and the hexahydrobenzofuran unit have been discussed. The approach to the spiroketal unit relied on the anomeric effect to provide a preference for the α anomer. The synthesis of the hexahydrobenzofuran units has been achieved in several different ways. After successful glycosylation and the little more troublesome deconjugation, the completion of the total syntheses of milbemycin β3 and avermectin A1a and B1a have been accomplished.

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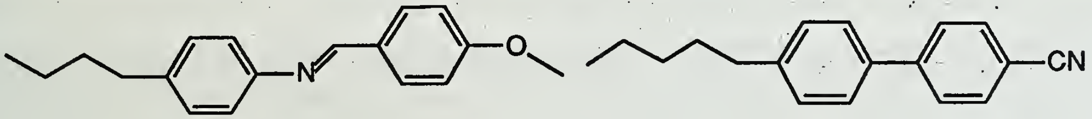
CHIRAL RECOGNITION IN LIQUID CRYSTALS: ORIGIN AND APPLICATIONS

Reported by Björn Sauerwein March 30, 1989

Since their discovery in 1888 by Reitzner, liquid crystals have been of interest to the organic chemist. The research has been centered mainly on the discovery of new mesogenic compounds. It is only recently, however, that chiral effects in these compounds are beginning to be understood.

BACKGROUND: WHAT ARE LIQUID CRYSTALS?

Liquid crystals (LCs) possess properties of both the liquid and the solid phases, and therefore are referred to as mesophases; compounds exhibiting this behavior are called mesogens. While being true fluids, they show a high degree of order; the long axes of the molecules are parallel to each other. A vector results pointing in a unique direction; it is called the director of the phase. About 5% of the known organic compounds,[1] typically linear ones with alkyl chains such as MBBA or BPC (Fig.1) form LCs at a temperature range just above their melting points.



MBBA **PCB**

Figure 1. Two typical mesogens: 4-Methoxy benzylidene 4'-butyl aniline (MBBA), 4-cyano 4' pentylbiphenyl (PCB).

LCs may be thought of as self-dissolved crystals. The alkyl chain acts as an inherent solvent while the remainder of the molecule is quasi-crystalline. They can be classified into three major structural types: smectic, cholesteric and nematic. Smectic LCs possess a two-dimensional order in which layers of parallel molecules are stacked on top of each other. The angle between the layer plane and the director varies between 30° to 90°. The degree of order for the smectic LCs is higher than for other classes of LCs. Consequently, they form at lower temperature, only just above the melting point of the solid. The visual appearance of the smectic phase is that of a highly viscous, turbid liquid.

Nematic LCs have the least degree of order. They are also referred to as one-dimensional because only one unique directional alignment exists. Besides that, they show no other intermolecular order. The nematic LC phase is slightly viscous and turbid.

A cholesteric phase can be formed either by a chiral mesogen or some other chiral influence like mechanically twisting the bulk phase. Here, the director rotates about an axis perpendicular to

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it which results in the formation of a helix. This helix is characterized by its pitch p, the distance at which the director has completed a full turn; typical values are 0.2 μm or greater.

OPTICAL EFFECTS

LCs show remarkable optical effects. Linearly polarized light, when propagated through a cholesteric LC parallel to its helical axis, is rotated in the helix screw sense with the value of the rotatory power two to three orders of magnitudes greater than in any other solid, liquid or gas; the molar rotation can reach values of up to 50,000.[3] If the wavelength of the linearly polarized light in the medium is equal to the helical pitch, then circularly polarized light with the handedness opposite of the helix is selectively reflected. This is achieved with efficiencies of up to 100% and gives rise to an extremely strong circular dichroism (CD). Also, strong CD for the material's chromophore, if present, is observed. These features can be used to detect and characterize the cholesteric phase.

Apart from ORD and CD, other methods for determining helicity and pitch have been developed. One of the most elegant is that reported by Grandjean[4] and Cano.[5] The technique involves placing a sample of the cholesteric LC in a wedged cell which had been previously wiped in one direction with an ordinary tissue; this results in the alignment of the director of the liquid crystal parallel to the direction of wiping. When viewed through a polarizing microscope, lines of dark and light (disclination lines) are observed that have a separation of p/2. Heppke and Oestreicher modified this to what is now known as the lens method.[6] They placed a drop of sample between a glass plate treated as above and a lens which had been rotated while pressed against a tissue. Then, when the sample is observed with a polarizing microscope, a double spiral with the handedness opposite to that of the helix of the cholesteric LC is observed. Equation 1 describes the relation between separation of the spiral arms and helical pitch:

$$\mathbf{r}^2 = \mathbf{R}\,\mathbf{p}\,\alpha \qquad \text{(eq. 1)}$$

where **r** is the radius of spiral arm at the angle α and **R** the radius of the lens used. The so-called droplet method[7] is based on the same principle and involves a drop of LC floating on the surface of an isotropic liquid.

INDUCTION OF CHIRALITY IN NEMATIC PHASES

Achiral molecules dissolved in cholesteric LC phases exhibit strong Liquid Crystal Induced Circular Dichroism (LCICD) indicating a strong interaction between guest and host. Moreover, the opposite effect is observed as well. Nematic LC phases can be transformed into cholesteric ones by doping them with a chiral substance;[8] the dopant does not even have to be a mesogen. In order to quantify the latter effect, the twisting power (β) has been introduced (eq.2).

$$\mathbf{1/p} = \mathbf{c}\;\mathbf{r}\;\beta \qquad \text{(eq.2)}$$

At low concentration of dopant the pitch **p** of the helix is inversely proportional to the mole fraction **c** of dopant and its enantiomeric purity **r**. The proportionality constant β is the twisting power, a positive sign indicating induction of a right handed helix.

MODELS FOR THE MODE OF ACTION

Unfortunately, there is no simple relationship between the handedness of the helix induced with either the absolute configuration or chiroptical measurements.[9] This is not surprising as there is no reason why the effect should follow an arbitrary ordering system; neither are interactions between molecules expected to parallel interactions of molecules with light. Early attempts to find a model for predicting the magnitude and screw sense of the induced cholesteric LC yielded a set of rules with limited scope. For example, Gray and McDonnel investigated the effects of a series of substituted biaryl cholesterogens (Fig. 2) and found a dependence of the helical sense with the number atoms spacing the chiral center from the aromatic system.[10]

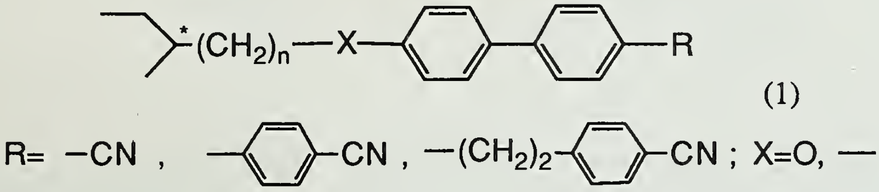
(1)

Figure 2

With the chiral center in the S configuration, a right handed helix is formed, if the number of groups is even; a left handed helix results resulted when it is odd. However, this is not transferable to different systems. Predictions made by this rule should always be checked by independent means.

A more systematic approach was advanced by Schrader et al who studied the effect of over a hundred chiral compounds in MBBA and other closely related nematic phases.[11] They proposed a model based on a priority scheme similar to the Ingold-Prelog system that ranks substituents by their effective volume. While in many cases this empirical model seems to hold, it fails to explain the observations by Gray mentioned above. Furthermore, some compounds are known to induce a different twist sense in different nematic LC phases.[12]

Saeva was the first to conclude that an empirical model can not reliably predict the direction or the magnitude of the effect.[2] He suggested that for a model to hold it has to consider the molecular interactions between the solvent and the solute. The first actual model based on this approach was proposed by Gottarelli and coworkers[13]. They investigated the cholesteric phases of MBBA induced by chirally substituted benzyl alcohols and found an almost perfect relationship between absolute configuration and helical screw sense. Linear dichroism showed that the molecular axes of solute and solvent were aligned parallel. This was attributed to a stacking overlap between one of the phenyl groups in MBBA and the alcohol. Polarized IR spectroscopy yielded evidence for a hydrogen bond between the imino nitrogen of MBBA and the hydroxyl proton perpendicular to the director. With these interactions, four arrangements between solvent and solute molecules are possible (Fig.3).

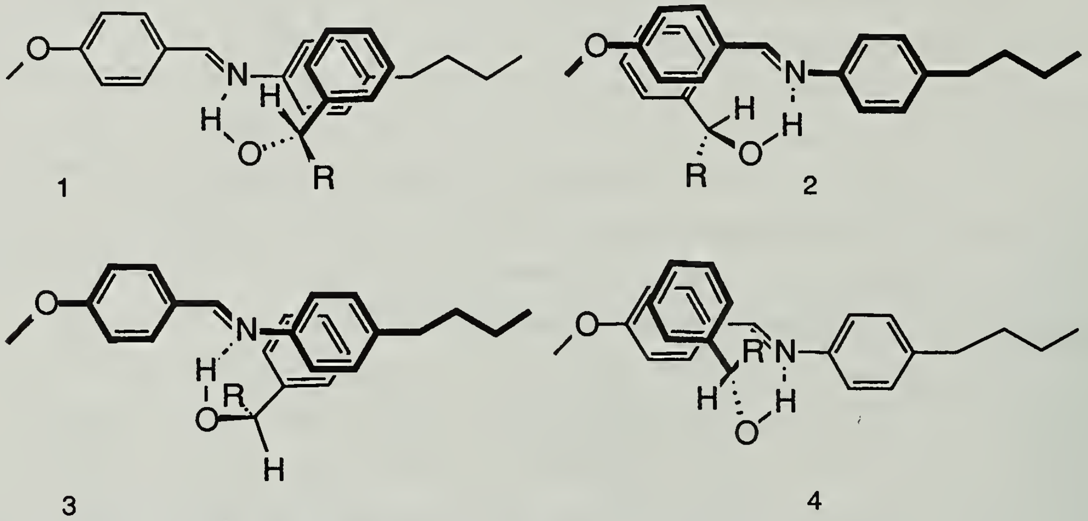

Figure 3. Possible stacking modes of S-1-phenylethanol in MBBA

The twist of the layers is achieved by stacking the next "solvent" molecule on top of the complex. As with Schrader's model, the relative sizes of the hydrogen and the substituent determine the direction of the twist. In this way, modes (1) and (2) give rise to right handed helical twisting; modes (3) and (4) cause a weak left handed twist. The effect in (1) and (2) is stronger since the bulkier substituent is closer to the geometrical center. For the same reason, interactions are more severe in (3) and (4), so that the conformations (1) and (2) are favored. This model is in accordance with the experimental data except for 2,2,2 trifluoro phenyl ethanol which shows a weak left handed twisting.

Pirkle and Rinaldi modified Gottarelli's model to account for the behavior of perfluorated alkyl substituents and to include aliphatic molecules.[14] While still assuming the presence of a hydrogen bond to the imino nitrogen, which is supported by strong experimental evidence, they proposed an interaction of the carbinyl hydrogen with one of the nuclei of MBBA, forcing the guest molecule into a fixed position with the two remaining substituents perpendicular to the long axis of MBBA. The twist in the macromolecular structure is then induced by the relative repulsion powers of the remaining two substituents rather than their relative sizes (Fig. 4). This assumes the perfluoroalkyl group to be more repulsive than the phenyl group, a fact which is supported by data in the literature.[15]

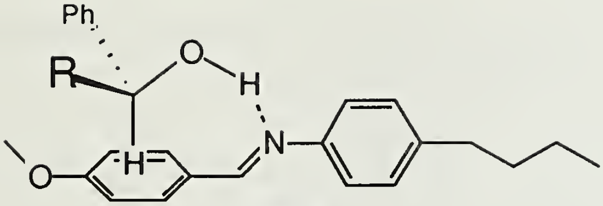

Figure 4

The "Pirkle - Rinaldi" model has been successfully used to assign the absolute configuration of various oxaziridines. However, exceptions from the model have been found,[14] and the perpendicular arrangement of the molecular axes seems to be rather unlikely. Also, the deviation from the predictions by Gottarelli's model in the perfluoroalkyl benzyl alcohols might be due to the operation of an anomeric effect for the trifluoro- and the hydroxyl groups (Fig.5).

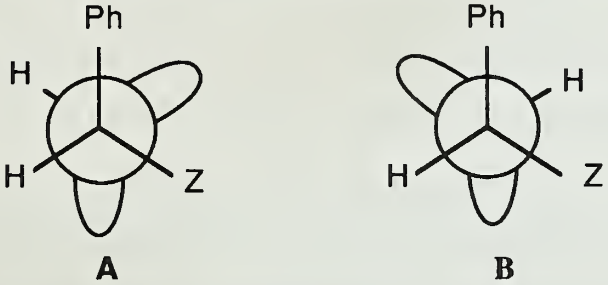

Figure 5. Newman projections of S-1-alkyl benzyl alcohol along the C-O bond. **A** and **B** correspond to stacking modes (1)/(2) and (3)/(4), respectively.

If Z = CF_3, an anomeric effect favors the otherwise unfavored confirmations (3) and (4) over (1) and (2) whereas in **B**, no anomeric effect is possible.

An equally systematic approach has more recently been used by Gottarelli and coworkers to find a working model for the induction of helicity by chirally distorted epoxides and thiiranes into MBBA[16]. These compounds show high rotating power specifically in that solvent (Table I).

Table I. Rotating powers in dependence of the solvent

Phase	Kind	β_M
MBBA	Schiff base	-42
Phase IV	Azoxy derivatives	-29
E7	di-and terphenyls	-11
Phase 1083	phenylcyclohexanes	-10
ZLI 1167	dicyclohexanes	-3

As for the case of the benzyl alcohols, Gottarelli and coworkers have assigned the molecular axes of the guest and the host to be parallel by UV linear dichroism spectroscopy. From crystal structure data it is apparent that the phenyl rings in the stilbene oxide derivatives reside in a 'propeller-like' conformation (Fig.6) [17]. MBBA itself exists in two rapidly interconverting chiral conformations with a similar 'propeller-like' shape; the dihedral angle between the phenyl groups is measured between 41 and 55 degrees.[18]

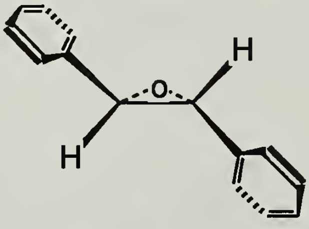

Figure 6

Based on these facts, Gottarelli et al. propose that the dopant binds to one conformer of the mesogen selectively. The same mechanism then operates on the second and the following molecular layers. This process has been termed conformational chirality transfer[16] and also accounts for effects observed in other systems: For example, the rotating power of some dopants is far higher than can arise from a single solvent molecule interacting with a single molecule of solute.[3]

As recently shown, conformational chirality transfer operates in biaryl systems as well.[19,20] Gottarelli and Solladie investigated a large variety of conformationally fixed bridged biaryl systems in the nematic PCB. They were able to show that the important feature in these compounds is the chirally tilted biaryl group, and that other changes in the structure had no or little effect on the twisting power.

CHIRAL RECOGNITION IN FERROELECTRIC SMECTIC PHASES

Tilted smectic phases (smectic C) of chiral compounds possess a macroscopic dipole moment, i.e. they are ferroelectric. The vector of polarization is perpendicular to both the layer normal and the director. Walba et al.[21] tried to elucidate the chiral recognition process giving rise to the ordering of molecules within the phase. They investigated compounds such as shown in figure 7 and argue that they exist in a zigzag conformation with the two alkyl chains less tilted towards the layer normal than the core.

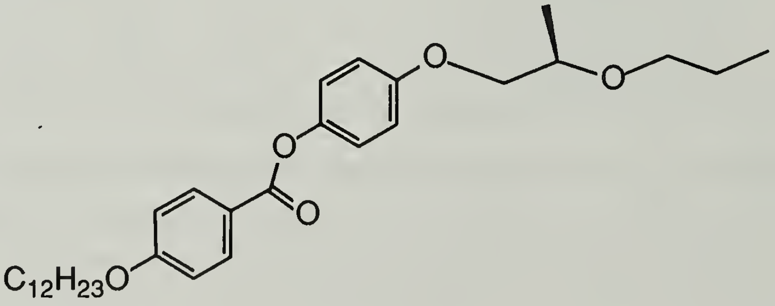

Figure 7

If the molecules reside in this binding site, which is shaped like a "bent cylinder",[21] predictions can be made regarding the direction and the magnitude of the ferroelectricity. In order to prove this, Walba et al. synthesized both diastereomers of 4'-(decyloxy)phenyl 4-[(S,S)-2,3-epoxy-1-fluorononyl]benzoate (Fig. 8).[22] For the compound fluorinated in the S configuration, a small positive polarization is predicted, whereas the compound fluorinated in the R configuration should induce a large negative polarization. This behavior is in fact seen.

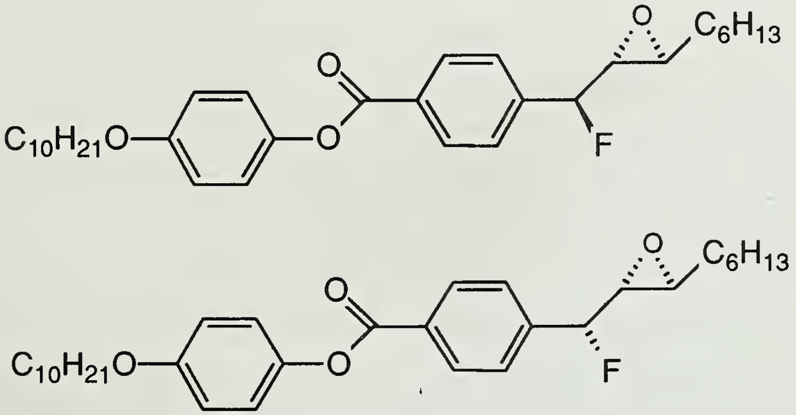

Figure 8

APPLICATIONS

The amplification of chiral induction into nematic LC phases has useful applications. Technical applications include optical displays, switching devices and optical memories, but the amplification of the rotation of polarized light by a chiral compound in a nematic LC phase is of interest especially to the organic chemist.

The extreme sensitivity of nematic LC phases towards chiral dopants has been exploited for analytical purposes. Korte[23] has used this technique to prove the chirality of only 3 μg of tyrosine methyl ester. The chiral induction method can even be used in combination with gas or thin layer chromatography; the quantities of material obtained by these techniques are sufficient. For example, Gottarelli et al. used the method for the determination of heroin.[24] They purified heroin by TLC and determined the amount by means of the lens method. From the magnitude of the pitch and the rotating power they determined the concentration of heroin present and found the detection threshold to be 0.38 μg. The same group has also been successful in proving the optical activity of asymmetrically deuterated compounds.[25] The specific optical rotation of these compounds is very small so that more standard chiroptical methods to determine their enantiomeric purity are either not applicable or require vast amounts of material.

Racemization reactions can be followed using LCs if the LC material used is stable at the required temperature. This method is more accurate and more convenient than conventional polarimetry, because of its higher sensitivity and the sample does not need to be weighed. Accurate measurements of racemization barriers have already been obtained this way.[26]

The chiral induction method can also be used to create new chiral centers, when a reaction is carried out in a cholesteric phase.[27,28] Even when the cholesteric phase is induced by mechanical twisting of the reaction vessel's walls, an enantiomeric excess (EE) of products has been seen. However, the observed EEs have thus far been very small (i.e. 0-7 %).

Certainly the greatest potential use of nematic LCs is in the determination of absolute stereochemistry. By using the models described in the previous section, absolute configurations of oxazines[14] and optically active binaphthyls[19] have been determined. If the model that emerged from these studies shown proves to be general, the technique could very well become a valuable addition to ORD and CD spectroscopy.

The LC method allows analytical distinction between cisoid and transoid binaphthalenes.[19] Those species are indistinguishable by ORD or CD; in this case the determination actually proves to be superior to the conventional methods.

It is expected that conformational chirality transfer is a general mode of action for inducted cholesteric phases. The development in this area will show if the model developed is actually valid in other systems apart from the ones already investigated.

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ARYLCYCLOPROPANE PHOTOCHEMISTRY: REACTIONS THAT INVOLVE CYCLOPROPANE RING OPENING

Reported by Kyung Mi Park April 6, 1989

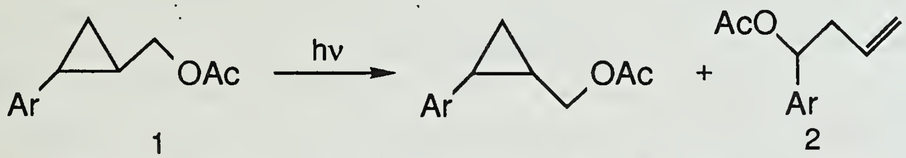
INTRODUCTION

Early studies of the photochemistry of arylcyclopropanes showed many interesting reactions. Recently, many studies on the mechanisms of photochemical reactions of arylcyclopropanes have been performed. It was revealed that the electron donating property[1] of cyclopropane rings and the polar and radical-like behavior of the excited state of arylcyclopropanes[2] are very important in the photochemistry of arylcyclopropanes. In this abstract, the recent mechanistic proposals for the photochemical reactions of arylcyclopropanes that involve the fission of the cyclopropane rings are discussed.

CHARGE TRANSFER

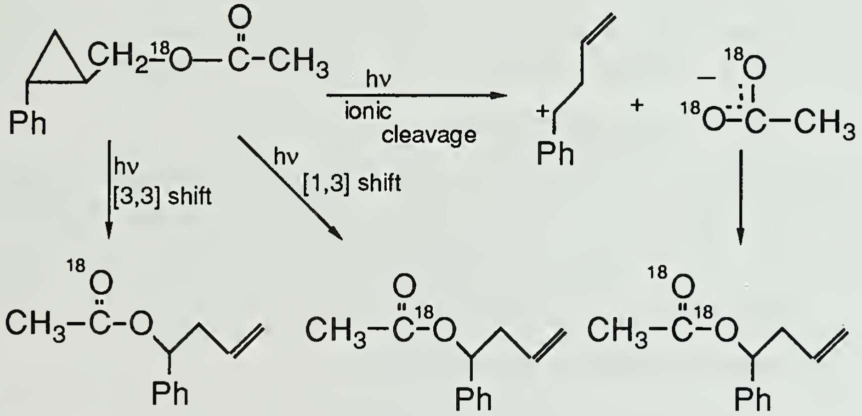
Hixson and co-workers studied the mechanisms of the reactions occurring from the singlet manifold of arylcyclopropanes by means of substituent effects. They studied the mechanism of the photochemical rearrangement of *trans*-(2-arylcyclopropyl)methyl acetates to 1-arylhomoallyl acetates(Scheme I).[3]

Scheme I



For this reaction, three possible mechanisms were considered. The total scrambling of the labelled oxygen in the photoproduct indicates that the ionic mechanism is dominant (Scheme II).[4]

Scheme II



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The irradiation of an acetone solution of *trans*-(2-arylcyclopropyl)methyl acetates gave only trans-cis isomerization. There were traces of other product as well, but in no case was the formation of homoally products detected. This result indicates that this reaction is a singlet process. Acetone acts as both solvent and triplet sensitizer.

However, for the ionic mechanism, the observed substituent effects are very unusual; electron-donating groups on the aryl rings have little effect on the rate or decrease it, whereas, electron-withdrawing groups which destabilize formed positive charge, increase it (Table I).

Table I

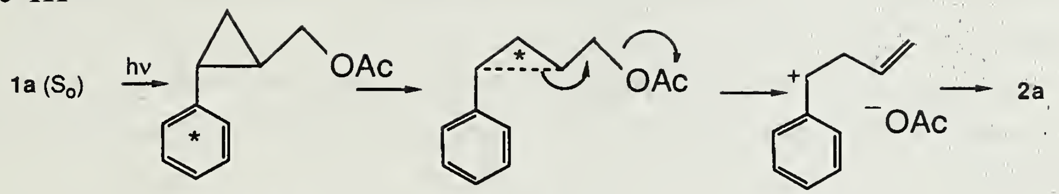
reactant	Φ	$10^{-6}k_r$	k_r(rel)
1a (Ph)	0.039	2.1	1.0
1b (*p*-MeOPh)	0.012	2.4	1.1
1c (*m*-MeOPh)	$\leq$0.002	<0.25	<0.12
1d (*p*-CH_3Ph)	0.026	1.4	0.67
1e (*m*-CH_3Ph)	0.010	0.44	0.21
1f (*p*-CNPh)	0.033	>55	>26
1g (*m*-CNPh)	0.094	>157	>75
1h (*m*-CF_3Ph)	0.088	140	67

To explain these results, a bimolecular electron transfer mechanism was considered. If the reaction proceeds by a single-electron transfer mechanism from a donor in solution to the aryl ring of the (2-arylcyclopropyl)methyl acetate, the rate increase with electron-withdrawing groups might be explained. However these reactions proceeded very well in many kinds of media (cyclohexane, ether, methanol, acetonitrile) and **1a** reacted only 50% faster in acetonitrile than in cyclohexane. Also, there was no rearrangement of either **1a** or **1h** when irradiations were carried out in the presence of the electron donor, such as N,N-dimethylaniline.

Hixson concluded that while the reaction involved ionic intermediates, carbocation formation was not the rate-determining step. He suggested a two-stage mechanism in which some step prior to ionization was rate-determining.

From spectroscopic studies, Becker and Griffin concluded that the spectroscopic singlet states of the phenylcyclopropanes are benzene-like and these benzene-like states may be converted to radical-like states.[5,6] In this radical-like state, the cyclopropane bond is lengthened and weakened, and exhibits both radical and ionic behavior. This diradical state (R) is postulated to mediate the observed photochemistry (Scheme III).

Scheme III



S$_1$(π,π*) R

In the qualitative state correlation diagram(Figure 1), π, π*and σ,σ* represent excited singlet states with excitation localized in the aromatic ring and cyclopropane ring, respectively. R is the nonspectroscopic diradical state.

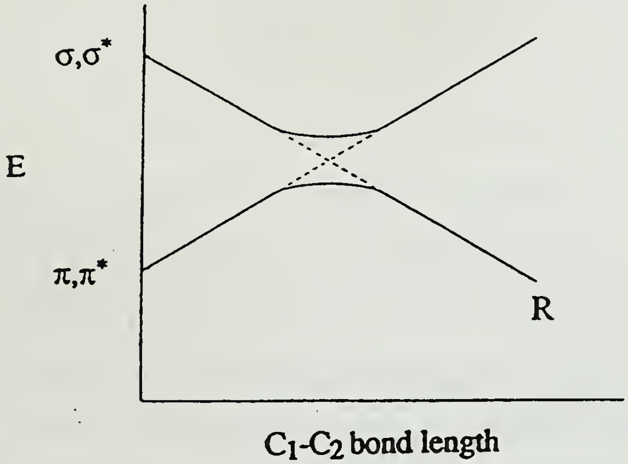


Figure 1

The increase in the energy of the π,π* state, and the decrease in the energy of the σ,σ* cyclopropane excited state with increasing length of the C$_1$-C$_2$ bond leads to an avoided crossing. So, the slowest step in the reaction of a molecule in the S$_1$ state is traversing the energy barrier leading to this avoided crossing.[7]

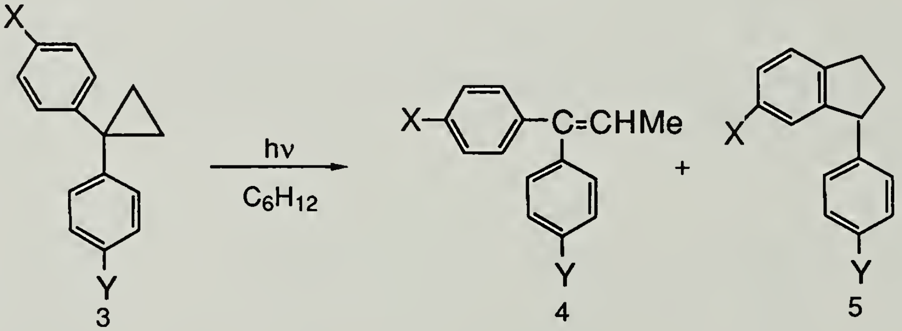
By UV spectroscopic study of conjugated arylcyclopropanes it was shown that the cyclopropane ring can act as an electron donor and the conjugative interaction between the rings is increased as the aromatic ring becomes more electron-withdrawing.[1] So, the substituents can affect the rate of the conversion from S$_1$ to R by their ability to promote charge transfer from the cyclopropane ring. This charge transfer is thought to accelerate the cyclopropane ring opening.

The rate decrease caused by electron-donating groups can be explained by their ability to donate electrons to the aromatic ring. This decreases the excited state electron donation from the cyclopropane ring.

There are two other singlet reactions of arylcyclopropanes which exhibit similiar charge transfer enhancement ; the formation of olefins and indans from 1,1-diarylcyclopropanes[8] and the 1,3-hydrogen migration of (alkyl-phenyl)cyclopropanes.[9,10]

Irradiation of 1,1-diarylcyclopropanes **3**, having substituents X and Y at the para positions of the aromatic rings, gave 1,1-diarylpropenes **4** and 1-arylindans **5** (Scheme IV).

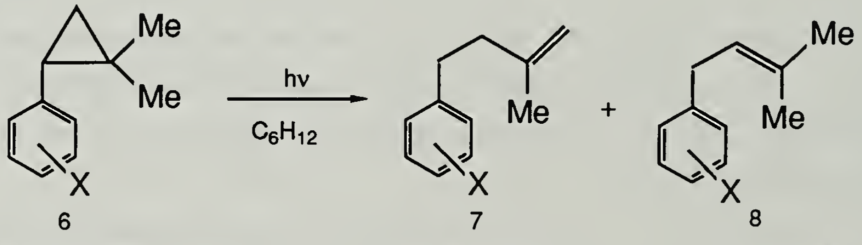
Scheme IV



For this reaction, Hixson suggested a mechanism similiar to that for the photochemical rearrangement of *trans*-(2-arylcyclopropyl)methyl acetates to 1-arylhomoallyl acetates. It involves conversion of the initially formed excited S_1 states to a diradical states R and subsequent reactions occur from these diradical states.

Irradiation of 1,1-dimethyl-2-arylcyclopropanes **6** gave 2-methyl-4-aryl-1-butene **7** by a 1,3-hydrogen migration. Formation of **7** is accompanied by lesser amounts of butene **8** derivatives. The fastest reacting compounds of those studied are **6a** and **6b**. The electron-donating methoxy group retards the reaction (Scheme V).

Scheme V

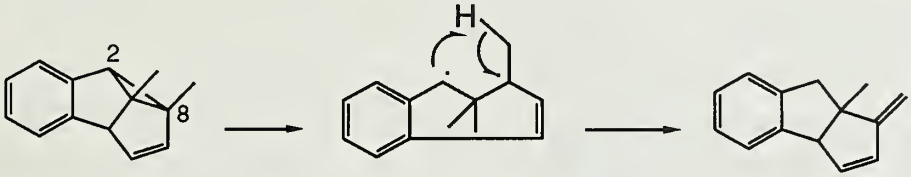


a, X=*p*-CF_3
b, X=*m*-CF_3
c, X=*p*-Me
d, X=*m*-Me
e, X=H
f, X=*m*-OMe

These similiar substituent effects for different overall processes support Hixson's conclusion strongly.

Bender studied the 1,3-hydrogen migration of 1,8-dimethylbenzosemibullvalene.[11] He suggested two possible pathways for the reaction; a concerted $[2\sigma_s+2\sigma_s]$ process and nonconcerted process. CNDO/2-CI calculations for changes in atom-atom interaction energies for the lowest singlet and triplet excited states of 1,8-dimethylbenzosemibullvalene concur with the nonconcerted pathway. Also the calculation showed that the cyclopropane bond between C_2 and C_8 is the most weakened relative to the ground state (Scheme VI).

Scheme VI

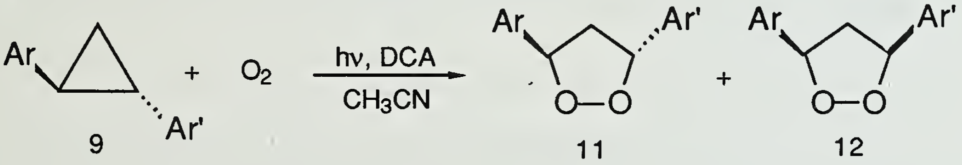


Even though there are differences in the magnitude of the response to aromatic substitution for these three reactions, they show basically the same substituent effect in spite of their differences in the electronic nature of the reactions. The difference may be explained by the fact that the observed reaction rates(k_r's) are the product of the rate of ring opening to diradical state R and the efficiency of conversion of R to product. The former is basically the same process in all reactions, but the latter is not and the difference in rate for different substituents is probably due to this.

ELECTRON TRANSFER

Electron transfer induced photooxygenation reactions are currently attracting much attention in organic chemistry. Mizuno and co-workers have studied the photooxygenation of 1,2-diarylcyclopropanes. Irradiation of an oxygen-saturated, dry acetonitrile solution of *trans*-1,2-bis(4-methoxyphenyl)cyclopropane(**9c**) in the presence of a catalytic amount of sensitizer 9,10-dicyanoanthracene(DCA) gave *trans*- and *cis*- 3,5-bis(4-methoxyphenyl)-1,2-dioxolanes in 95% yield(Scheme VII).[12,13]

Scheme VII



Cis-1,2-bis(4-methoxyphenyl)cyclopropane(**10c**) was irradiated under similiar conditions. Rapid isomerization of **10c** to **9c** occurred during the initial stage of the reaction.[14] Further irradiation of the reaction mixture yielded **11c** and **12c** in a ratio identical with that obtained in the photoreaction of **9c**. The irradiation of other *trans*-1,2-diarylcyclopropanes(CP) having electron-donating substituents gave the corresponding 1,2-dioxolanes in high yield. However, the photoreaction of less electron-rich 1,2-diarylcyclopropanes, which have a higher oxidation potential than **9a-g,** gave various oxidation products in low yield after prolonged irradiation (Table II).

Table II

compound		E^{ox}(V)	ΔG(kJ mol^{-1})
9a	Ar=4-$Me_2NC_6H_4$, Ar'=4-$MeOC_6H_5$	---	---
9b	Ar=4-$Me_2NC_6H_4$, Ar'=C_6H_5	0.25	-132.2
9c	Ar=Ar'=4-$MeOC_6H_4$	0.55	-103.2
9d	Ar=Ar'=3,4-$(MeO)_2C_6H_3$	0.55	-103.2
9e	Ar=4-$MeOC_6H_4$, Ar'=4-MeC_6H_4	---	---
9f	Ar=4-$MeOC_6H_4$,Ar'=4-ClC_6H_4	---	---
9g	Ar=4-$MeOC_6H_4$, Ar'=C_6H_5	0.75	-83.9
9h	Ar=Ar'=4-MeC_6H_4	0.90	-69.5
9i	Ar=Ar'=4-ClC_6H_4	1.06	-54.0
9j	Ar=Ar'=C_6H_5	0.14	-93.6
DABCO		0.31	-126.4

The fluorescence of DCA in acetonitrile was efficiently quenched by **9a-g** at nearly the diffusion controlled rate. The free energy changes for the electron-transfer from these quenchers to excited DCA ($^1DCA^*$) were estimated to be negative (Table II).[15]

The reactivity of **9c** in the DCA-sensitized photooxygenation is strongly depended on the solvent polarity. The relative rate for the formation of **11c** and **12c** decreased with decreasing solvent polarity ($CH_3CN>C_2H_5CN>n\text{-}C_3H_7CN$), and no product was formed in benzene or methylene chloride. The formation of **11c** and **12c** in the presence of DCA in acetonitrile was efficiently quenched by the addition of radical quencher, such as 1,4-diazabicyclo[2.2.2]octane (DABCO) or triethylamine (TEA).

These results led Mizuno to conclude that in the DCA-sensitized photoreaction of arylcyclopropanes (CP), the ion radical pair [$DCA^{-\cdot}$...$CP^{+\cdot}$] is produced spontaneously upon excitation of DCA. The solvent effect also supports the involvement of electron transfer and participation of an ion radical pair in the photooxygenation of CP in polar solvent.[16]

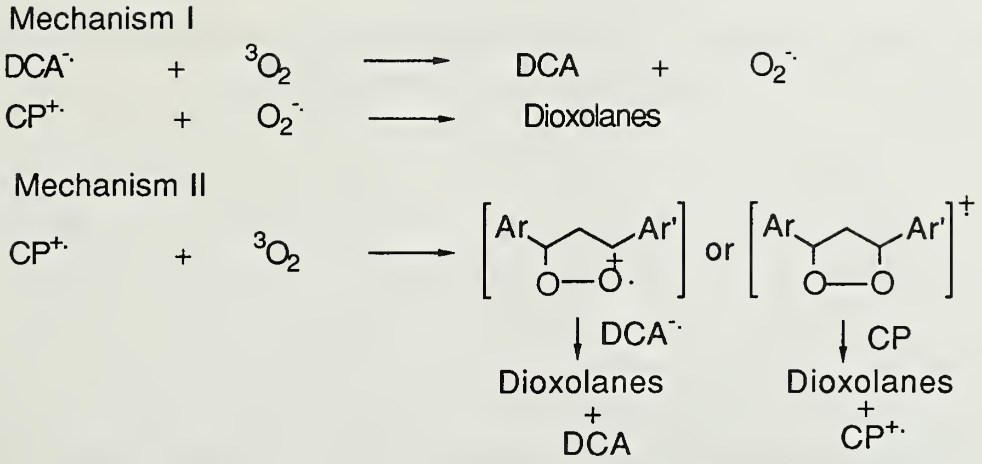
The suggested mechanisms are shown in scheme VIII.

Scheme VIII

$$\mathrm{DCA} \xrightarrow{h\nu} {}^1\mathrm{DCA}^*$$

$${}^1\mathrm{DCA}^* + \mathrm{CP} \longrightarrow [\mathrm{DCA}^{-\cdot} \cdots\cdots \mathrm{CP}^{+\cdot}]$$

$$[\mathrm{DCA}^{-\cdot} \cdots\cdots \mathrm{CP}^{+\cdot}] \longrightarrow \mathrm{DCA}^{-\cdot} + \mathrm{CP}^{+\cdot}$$



Mechanism I involves the reaction of $Cp^{+\cdot}$ with $O_2^{-\cdot}$, which may be generated by electron transfer from $DCA^{-\cdot}$.[17] In mechanism II, the electron transfer occurs from Cp or $DCA^{-\cdot}$to the intermediate which is generated by the reaction between $Cp^{+\cdot}$ with $^3O_2$. The chain mechanism was supported by the fact that the reaction of **9c** with $^3O_2$ in the presence of a catalytic amount of $Ph_3C^+BF_4^-$ in acetonitrile in the dark gave **11c** and **12c** in 60-70% yield. Also, the quantum yields for the formation of **11c** and **12c** exceed one. The study about the exact structure of $CP^{+\cdot}$ has not been done yet, even though it was reported that the isomerization of **9j** via its cation radical occurred through the break of the C-C bond of $CP^{+\cdot}$.[18]

The DCA-sensitized photooxygenation of the arylcyclopropanes is accelerated by the addition of aromatic hydrocarbons, such as phenanthrene and biphenyl or metal salts, such as $LiBF_4$ and $Mg(ClO_4)_2$. However, the product ratio remains unchanged. Also, the quantum efficiency in the presence of these additives is much higher than that in the absence. This enhancement can be explained by the effective formation of solvent seperated $Cp^{+\cdot}$ and also, by the suppression of back-electron transfer from $DCA^{-\cdot}$ to $Cp^{+\cdot}$ by π-complexation or ionic interaction.[19,20,21]

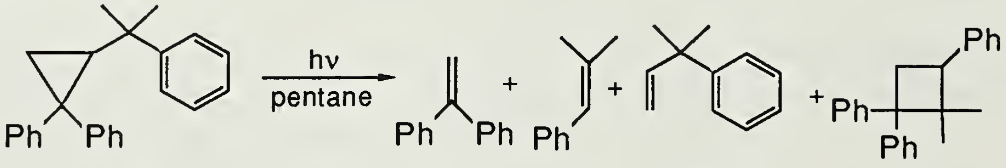
ARYLCYCLOPROPYL-π-METHANE REARRANGEMENT

The aryl version of the cyclopropyl-π–methane rearrangement has been studied by Zimmerman and co-workers. In 1975, they reported the first example of the reaction.[22] Irradiation of 3-(2,2-diphenylcyclopropyl)-3-methyl-1,1-diphenyl-1-butene gave 1,1-diphenylethylene and 4-methyl-1,1-diphenyl-1,3-pentadiene in addition to 2-methyl-1,1-diphenyl-1-propene and 1,1-diphenylbutadiene as secondary photochemical product.

Recently, the photochemistry of 2-(2,2-diphenylcyclopropyl)-2-phenylpropane **13** was reported.[23] Direct irradiation of arylcyclopropylmethane **13** gave 1,1-diphenylethene and 1-

phenyl-2-methyl-1-propene as products in addition to the ususal fragmentation products, diphenylcarbene and 3-methyl-3-phenyl-1-butene (Scheme IX).[24]

Scheme IX

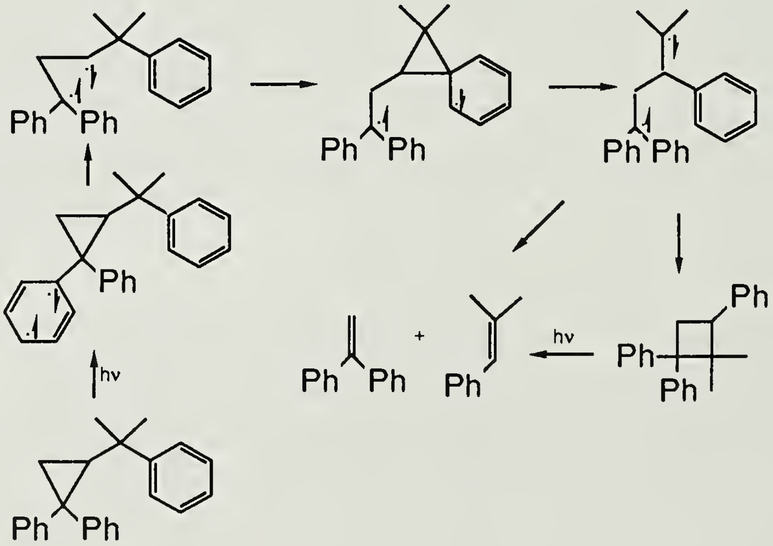


13 14 15 16 17

From the sensitization experiment, it was shown that only the singlet excited state is reactive for the arylcyclopropyl-π-methane reaction. Triphenylcyclobutane **17** was considered as a potential reaction intermediate because independent direct irradiation of this compound gave only diphenylethylene **14** and phenylisobutylene **15**. The dynamic isotope dilution method was used to determine the ratio of a direct (S → P type) versus indirect (S → I → P) mechanism.[25] The result gives the ratio between the two mechanistic pathways S → P and S → I → P as 91:1 (Scheme X).

The most interesting fact about this reaction is that the preference for 1,4-(2,3)-fragmentation over closure to cyclobutane product exhibited by the singlet of 1,4-diradicals. MNDO-CI and ab initio calculation show central bond stretching of the tetramethylene 1,4-diradical. For S_0, the open diradical leads to the Grob fragmented pair of ethylenes.[26] In contrast, the S_1 diradical proceeds toward cyclobutane formation.

Scheme X



Thus, cyclobutane formation is expected from S_1 and Grob fragmentation is anticipated from S_0. The present system is dominated by Grob fragmentation and the small amount of cyclobutane formation derives from the initial S_1 excited state formed on direct irradiation. The photochemical cleavage of the cyclobutanes occurred in a regioselective manner and it seemes to be that the controlling factor is the formation of the lowest energy diradical.

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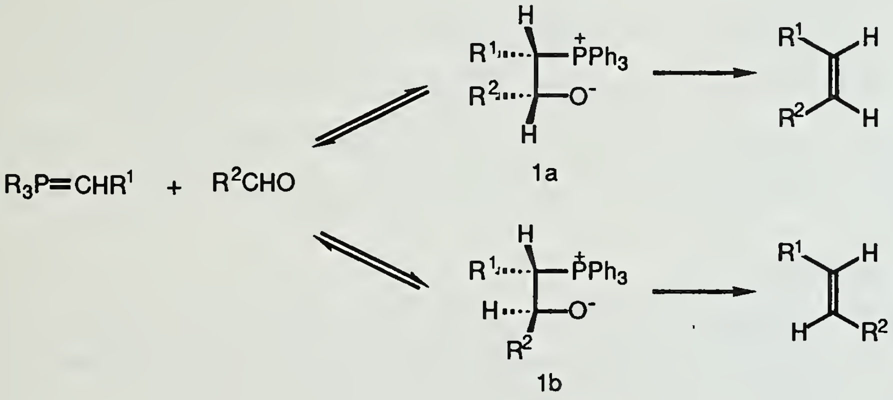
THE MECHANISM OF THE WITTIG REACTION

Reported by Neil G. Almstead April 13, 1989

INTRODUCTION

In 1953 Georg Wittig added benzophenone to methylidenetriphenylphosphorane producing 1,1-diphenylethylene and triphenylphosphine oxide[1]. The mechanism initially proposed by Wittig for this reaction which now bears his name involved the formation of a purely covalent oxaphosphetane intermediate. The Wittig reaction is one of the most widely used methods for carbon-carbon bond formation available. High *E* or *Z* selectivity for olefin formation can be obtained depending upon the reaction conditions. It was discovered that addition of lithium salts to the reaction drastically affected the stereochemical outcome. In the presence of lithium salts, *E* olefins are formed predominantly. In light of these findings, a mechanism was proposed which included the formation of a zwitterionic intermediate, termed a betaine[2]. It was thought that the addition of lithium salts would stabilize the betaine intermediate, allowing it to equilibrate and thus give the thermodynamically favored *trans*-olefin. This mechanism, Scheme I, requires formation of *cis*-olefins to be the kinetic process while *trans*-olefins are formed by the thermodynamically controlled process.

Scheme I



If the betaine is not stabilized by lithium salts, collapse to form the *cis*-olefin with elimination of phosphine oxide is faster than equilibration. If lithium salts are present, equilibration occurs to the more stable *trans*-betaine with subsequent elimination of phosphine oxide to form the *trans*-olefin. Further studies have recently been undertaken to elucidate the mechanism of the Wittig reaction and are described within.

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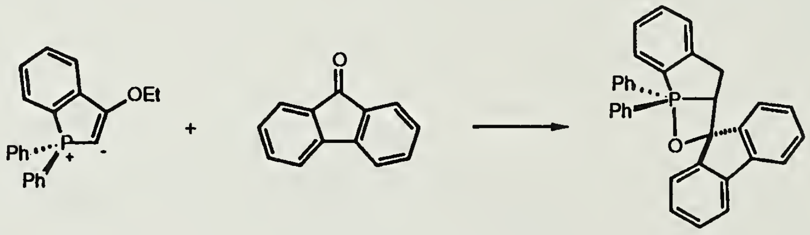
NEW MECHANISTIC STUDIES

Oxaphosphetanes were first observed spectroscopically by Vedejs in 1973 by a low temperature NMR study of the Wittig reaction[3]. A filtered solution of the ylide from ethyltriphenylphosphonium bromide and *n*-butyllithium was added to a small excess of cyclohexanone at -70°C. A single sharp signal was observed at δ_{31P} 66.5 PPM. This high field shift ruled out the presense of tetravalent phosphorous species such as betaines, ylides, or phosphine oxides, but is consistent with pentavalent phosphorous. It was earlier thought that oxaphosphetanes were high energy intermediates relative to betaines and were only found in the decomposition of betaines into phosphine oxides and alkenes[4]. The spectroscopic observation and the isolation of stable oxaphosphetanes invalidates this arguement. Bestmann[6] and others[7] have isolated stable oxaphosphetanes and X-ray structure analysis has been performed on these crystalline intermediates. Oxaphosphetane **2** (Scheme II) is a stable crystalline compound which decomposes upon heating to form olefin products. The geometry around phosphorous was thought to be trigonal-bipyramidal and this was confirmed by X-ray analysis. Betaines have never been isolated or spectroscopically identified as intermediates in reactions of non-stabilized ylides with aldehydes or ketones[7].

Scheme II



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Schlosser Mechanism

Schlosser studied the mechanism of the Wittig reaction and concluded that steric crowding in the transition state determines the overall selectivity of the reaction[8]. The bulky phenyl groups attached to phosphorous are pushed away by substituents attached to the phosphorous ylide. According to Schlosser the other equatorial phenyl ring will be only slightly out of plane, neccessitating an approach of the aldehyde from the least sterically congested side. The transition state proposed by Schlosser is shown in Figure I.

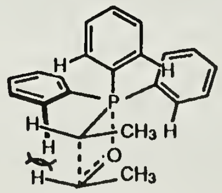


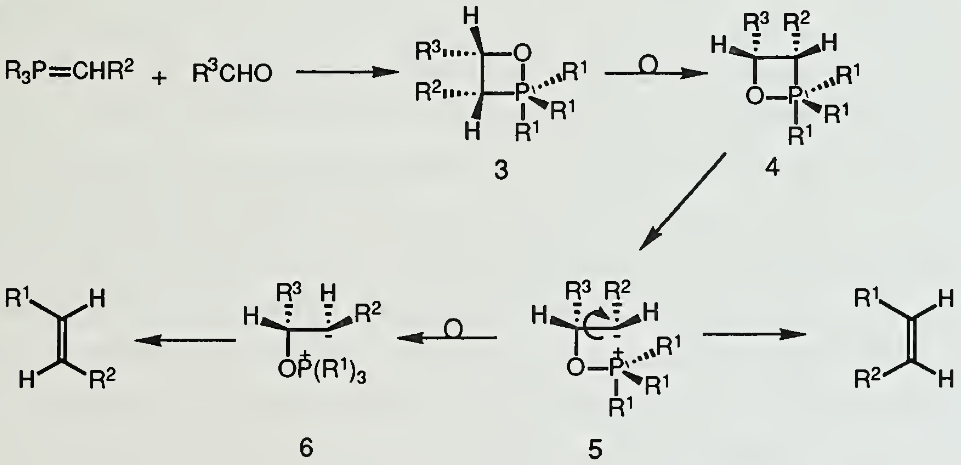
Figure 1

Schlosser describes the formation of the oxaphosphetane as being a concerted process. The selectivity found in the reaction is explained by steric crowding in the transition state leading to oxaphosphetane formation. If oxaphosphetane formation is reversible, equilibration could occur to form the more stable trans isomer. When the phenyl substituents on phosphorous are replaced by smaller groups such as ethyl the resulting *Z/E* selectivity would be expected to decrease. This hypothesis was later confirmed experimentally by Vedejs[9]. Schlosser felt that betaines are not intermediates on the pathway towards olefin formation unless lithium salts are added because they never have been observed spectroscopically. The formation of trans-olefins when LiBr is added is accounted for by equilibration of betaines to form the thermodynamically more stable trans betaine.

Bestmann Mechanism

Bestmann described a mechanism for the Wittig reaction (Scheme III) which involves an initial (2 + 2) cycloaddition of the ylide and aldehyde to form an oxaphosphetane intermediate[10]. Formation of a betaine intermediate was not included because of kinetic evidence against a multi-step process for the formation of **3**. Giese has studied the effect of substituents on the phenyl ligands of phosphorous[11]. His data indicates that the rate-determining step in the Wittig reaction is the one-step formation of an oxaphosphetane. The formation of the oxaphosphetane **3** can be rationalized by an approach of the ylide to the carbonyl at the Burgi-Dunitz angle of 107°[11]. According to Bestmann, rotation around the newly forming C-C bond takes place in such a manner that the P-O bond forms simultaneously, giving the oxaphosphetane **3**. The mechanism for the preferential formation of *cis*-oxaphosphetanes is not well known according to Bestmann. Steric hindrance in the transition state leading to the formation of oxaphosphetanes could explain the observed *cis* selectivity[12].

Scheme III



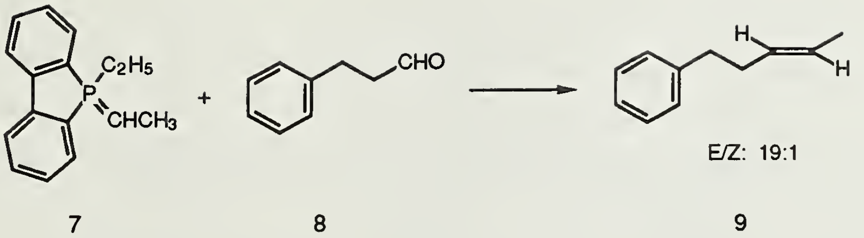
The initially formed oxaphosphetane **3** contains an oxygen atom which is in an apical position on phosphorous, an arrangement based upon the rules governing attack and leaving of nucleophiles during the reciprocal formation of tetra and pentacovalent phosphorous as described by Marquarding[13]. Breaking of a C-P bond leading to the decomposition of the oxaphosphetane intermediate can only occur when the C-P bond becomes apical. Pseudorotation of the ligands around phosphorous gives oxaphosphetane **4** with oxygen equatorial to phosphorous. The C-P bond breaks without a simultaneous cleavage of the C-O bond to form the betaine **5**.. The breakdown of the betaine intermediate depends upon the electronic nature of the substituents attached to phosphorous. When R^2 is electron donating and R^1 is phenyl the lifetime of the betaine is short, and formation of cis olefins is observed. When R^2 is electron withdrawing and R^1 is phenyl, the lifetime of the betaine is prolonged, and rotation around the C-C bond leads to the thermodynamically more stable betaine **6** and finally the *E*-olefin. The origin of the high *cis*-selectivity found with non-stabilized ylides was not explained.

Wittig reversal

Vedejs studied the reversibility and equilibration of the Wittig reaction and concluded that two distinct pathways for the formation of olefins are possible, dependent upon the addition of lithium salts[14]. For salt-free Wittig reactions the proposed mechanism invokes the formation of an oxaphosphetane with subsequent breakdown to form alkenes. Wittig reactions with added LiBr form betaine-lithium halide adducts. These betaine-lithium halide adducts could either be initially formed by an ionic addition process, or from ring opening of an oxaphosphetane lithium complex. The stereochemistry of alkene formation is affected by LiBr in the initial condensation step, and not by equilibration of the resulting oxaphosphetane. The exact site of lithium halide coordination is not well known, but coordination of Li^+ to the carbonyl group of an aldehyde or ketone, or the involvement of $Ph_3P^+CHRLiX^-$ are possibilies[5].

Highly *E* selective Wittig reactions were thought to be the result of Wittig reversal which will give the thermodynamically favored product. Kinetic control in the Wittig reaction involves almost no Wittig reversal and is found with non-stabilized salt free ylides. Vedejs observed salt-free Wittig reactions where the kinetic *cis/trans* preference for disubstituted oxaphosphetane formation was as high as the final *Z/E* ratio of olefin formed. Wittig reactions that are selective for Z olefins are thought to be under kinetic control because no equilibration of intermediates has been observed. Salt-free Wittig reactions that are highly *E* selective were also studied by Vedejs[15]. The nonstabilized ylide **6** was reacted under salt-free conditions at low temperature and the course of the reaction observed by NMR (Scheme IV). The adduct formed by this reaction was observed to be unchanging by NMR until the temperature of olefin formation is reached. The final *E/Z* ratio of products (95/5) was the same as the ratio of ^{31}P oxaphosphetane signals observed by NMR. No equilibration of intermediates or Wittig reversal was observed for this reaction. Vedejs concluded

Scheme IV



that all salt-free Wittig reactions of unbranched aldehydes are kinetically controlled regardless of the product olefin geometry.

Maryanoff has also studied the Wittig reaction by low temperature NMR spectroscopy in an attempt to develop a mechanistic understanding of the reaction. The observation of oxaphosphetane diastereomers by ^{31}P and ^{13}C NMR would provide a uselful tool to probe stereochemical aspects of the Wittig reaction[16]. Benzaldehyde reacts with the ylide prepared from lithium hexamethyldisilazane and *n*-butyltriphenylphosphonium bromide to give a mixture observed at -78°C by ^{31}P NMR. Integration of the oxaphosphetane resonances gave a 3.8:1 ratio of *cis* and *trans* diastereomers. Upon warming to -25°C the oxaphosphetane resonances disappeared with the appearance of triphenyl phosphine oxide. The ratio of remaining oxaphosphetane became enriched in *trans* oxaphosphetane over time, reaching a 1:1 ratio near the end of the reaction. The final *Z*/*E* olefin ratio of 1.5:1 does not reflect the initial 3.8:1 ratio of oxaphosphetanes observed by NMR spectroscopy. Maryanoff explained the change in *Z*/*E* selectivity by equilibration of the oxaphosphetanes. A greater proportion of *E* olefin was found on workup than was reflected in the original amount of *trans*-oxaphosphetane observed by NMR spectroscopy. This *cis* and *trans*-oxaphosphetane equilibration was termed stereochemical drift by Maryanoff[17].

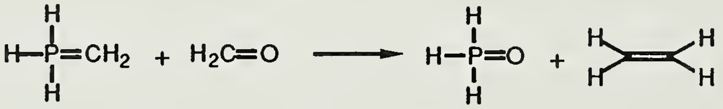
When heptanal reacts with the ylide generated from *n*-butyltriphenylphosphonium bromide and lithium hexamethyldisilazide oxaphosphetanes in a 5.8:1 *cis* to *trans* ratio were observed at -78°C. Warming the mixture gave the same 5.8:1 ratio of olefins as was observed for the oxaphosphetanes, indicating that no stereochemical drift had occured. When oxaphosphetane decomposition was 90% complete, a 1.7:1 ratio of *cis* and *trans*-oxaphosphetanes was observed. Maryanoff estimated that the *cis*-oxaphosphetane decomposed to olefin about three times faster than the corresponding *trans* isomer.

Aromatic aldehydes were found to undergo equilibration at a rate competitive with the rate of decomposition in the presence of lithium salts. Aliphatic aldehydes were also studied, and did not equilibrate in the presence of lithium salts. Maryanoff states that the principal effect of lithium salts is to alter the relative rates of *cis* and *trans* oxaphosphetane formation from the corresponding ylide and aldehyde[17]. Under salt-free conditions, no equilibration of the oxaphosphetane intermediates was observed for either aromatic or aliphatic aldehydes.

Theoretical studies

Computational work on the Wittig reaction has been described by Eisenstein and Volatron as well as by Bestmann. Eisenstein studied the Wittig reaction by means of *ab initio* calculations under salt-free conditions. The model used for the theoretical study is shown in Scheme V[18].

Scheme V



Oxaphosphetanes were found to be the only stable intermediates in the Wittig reaction. The first intermediate formed is an oxaphosphetane with oxygen apical to phosphorous. An orbital symmetry allowed concerted (2s + 2s) cycloaddition of the aldehyde and ylide is responsible for the formation of the oxaphosphetane. This oxaphosphetane was found to be more stable by 4.2 kcal/mole than the oxaphosphetane with carbon at the equatorial position of phosphorous. Pseudorotation of the oxaphosphetane will lead to a less stable isomer where C-P bond cleavage becomes a lower energy process. Ring opening of the less stable oxaphosphetane gives the olefin. The reversibility of the Wittig reaction was also studied by Eisenestein. It was found that more energy was required to go back to starting materials than to go on to products. Betaines were not found to be intermediates in the reaction pathway.

According to Eisenstein, the planarity of the oxaphosphetane intermediate characterize a concerted (2s + 2s) reaction[18]. The frontier orbitals of the two reactants are shown in Figure II.

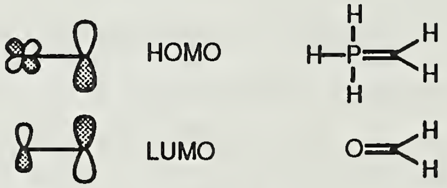
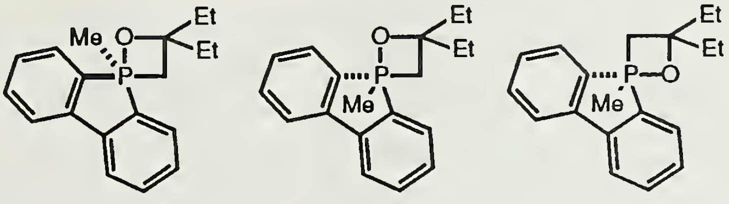


Figure 2

The HOMO of the ylide is a bonding combination of the p orbital on carbon with a phosphorous d orbital and the orbital coefficient density is concentrated on carbon. The orbital coefficient density of the LUMO of formaldehyde is also concentrated at carbon. As a consequence, the overlap between the two orbitals is significant, indicating that the (2s + 2s) cycloaddition is an allowed process. The product olefins are formed from a concerted (2s + 2s) cycloreversion[18].

Oxaphosphetane Pseudorotation.

Oxaphosphetane pseudorotation was studied by Vedejs with low temperature NMR spectroscopy experiments[19]. Oxaphosphetanes with apical oxygen have been shown computationally to be the most stable species in the gas phase, but have not been proven to be the most stable species found in solution. The study showed that at -53^{o}C oxaphosphetanes **10** and **10'** slowly equilibrated, but **11** was never seen (Figure III).



10 10' 11

Figure 3

These structures can be assigned by their individual C-P coupling constant. Equatorial sp^2 carbons in a trigonal bypyramidal arrangement around phosphorous have a characteristically large ^{13}C-^{31}P coupling constant ($J_{P\text{-}C}$ = 132 Hz) while apical carbons should have $J_{P\text{-}C} < 20$ Hz[20]. Only the larger coupling constant was observed, indicating that the oxaphosphetane with oxygen apical to phosphorous is preferred. Vedejs cautions that the absence of the oxaphosphetane with carbon apical to phosphorous by NMR does not rule out its role in the decomposition to olefins. The energy required for pseudorotation was found to be much less than that required for decomposition to olefins. This indicates that the rate limiting step in the Wittig reaction is decomposition to olefin and not pseduorotation of oxaphosphetanes.

Transition state geometry

Vedejs explained the selectivity found in the Wittig reaction by the position of the transition state along the reaction pathway[9]. Both *cis* and *trans*-selective salt-free Wittig reactions are said to be kinetically controlled. *Cis*-selective Wittig reactions cannot have product-like transition states, because *trans*-disubstituted oxaphosphetanes are more stable than the corresponding *cis* isomers. The decomposition of *cis* and *trans*-oxaphosphetanes was studied by NMR spectroscopy. The *cis*-oxaphosphetanes were consistently found to decompose faster than *trans*-oxaphosphetanes. *Trans*-oxaphosphetanes must therefore be thermodynamically more stable than the *cis* isomers. The transition state leading to the formation of the oxaphosphetane intermediate determines the stereochemistry of the final products in these kinetically controlled reactions. Planar geometry in the transition state for the cycloaddition is the simplest possible arrangement as shown be Eisenstein[18]. This geometry does not account for the steric bulk of the phosphorous ligands or of the aldehyde substituents. In an early transition state where phosphorous rehybridization has not occured, these steric interactions would be most important, leading to the possibility of a puckered or nonplanar transition state.

Vedejs has studied the transition state geometry of the Wittig reaction by using X-ray coordinates of representative ylides obtained from the Cambridge crystallographic data base[9]. This data was altered to account for differences between solid-state and solution geometry. *Cis* and *trans*-selective transition states are shown in Figure IV for salt-free Wittig reactions.

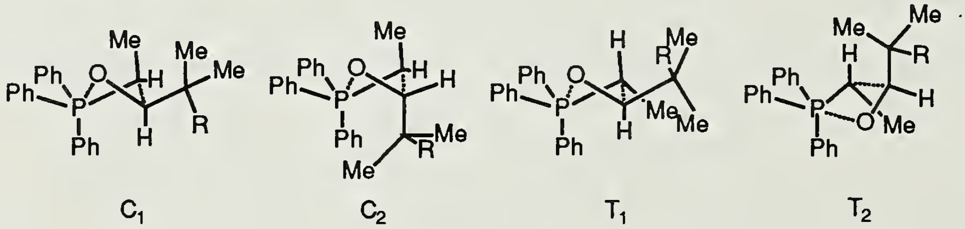


Figure IV

The *cis*-selective transition state C_1 is thought to be favored over C_2 because of less severe 1,3-interactions. In C_2 the alkyl substituents attached to the aldehyde are in a pseudoaxial position. This alkyl substituent can encounter one of the phenyl groups also in a pseudoaxial orientation, destabilizing the transition state. With C_1 the pseudoaxial methyl group of the ylide has no severe 1,3-interactions because the other pseudoaxial site is occupied by oxygen lone pairs. In the proposed *trans*-selective transition states, T_1, the tertiray alkyl group of the aldehyde and the α–CH_3 group of the ylide occupy the same pseudoequatorial plane, destabilizing the transition state. The other *trans*-selective transition state, T_2, has a more planar arrangement of ligands, increasing the possible 1,3 interactions with the ligands on phosphorous. In a late transition state, the hybridization at phosphorous will change from sp^3 to dsp^3, with an appropriate change of the phosphorous bond angles to 120°[9]. The *trans*-disubstituted oxaphosphetane is more stable than the *cis* isomer because of the change in phosphorous hybridization. The 1,3 interactions with the phosphorous ligands diminish when the hybridization changes because of an increase in distance between the phosphorous ligands and the substituents on the aldehyde.

Studies of substituent effects on phosphorous have been completed for reactions of non-stabilized ylides by Vedejs. These results are shown in Table I[9].

Table I

LZP=CHR Z/E Selectivity with Aldehydes

			$Ph(CH_2)_2CHO$	$PhCH_2C(Me)_2CHO$
L	Z	R	Z/E	Z/E
Ph_2	Ph	Me	16:1	>99:1
Ph_2	*t*-Bu	Me	17:1	99:1
Ph_2	*i*-Pr	Me	1:4.6	1:1
Ph_2	Et	Me	1:2.3	5.7:1
Et_2	Ph	Me	1:1.8	1.3:1
Et_2	Et	Me	1:2	1:9

When all of the ligands on phosphorous are phenyl, the *cis*-selectivity for the reaction is high. Replacement of a phenyl ligand by ethyl results in a significant decrease in the *cis*-selectivity of the reaction. Replacing more than one phenyl ligand by ethyl results in little difference in selectivity. Sterically demanding ligands on phosphorous prefer a *cis*-selective transition state because of possible 1,3 interactions with the aldehyde. Conformationally restricting the groups around phosphorous resulted in a very *trans*-selective reaction. The substituents on the ylide now have a *trans* arrangement in the transition state without significant steric interactions with the ligands on phosphorous.

CONCLUSION

The Wittig reaction can be characterized by two different mechanisms, dependent upon the presence of lithium salts. If lithium salts are not present, a non-stabilized ylide could react with an aldehyde or ketone *via* a (2s + 2s) cycloaddition to form an oxaphosphetane intermediate. This intermediate can either decompose into olefin, undergo pseudorotation to a less stable oxaphosphetane which will decompose to olefin, or revert back to starting materials. When lithium salts are present the exact mechanism is somewhat unclear. Lithium salts may coordinate to the newly formed oxaphosphetane or to the aldehyde before cycloaddition. It is thought that the stereochemistry of the reaction is decided in the initial cycloaddition and not by equilibration of the resulting oxaphosphetane.

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I. RECENT DEVELOPMENTS IN THE FIELD OF STEROID HORMONES: ACADEMIC VS. INDUSTRIAL STEROID SYNTHESES

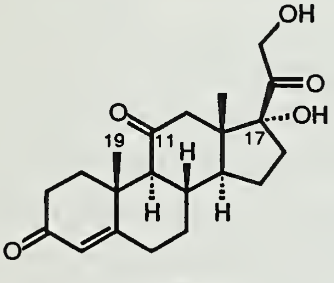
II. THE ANTIPROGESTIN STEROID RU 486: SYNTHESIS AND APPLICATION TO HUMAN FERTILITY CONTROL

Reported by Olivier Nicaise April 17, 1989

INTRODUCTION

Steroid hormones[1] are essential to human life. They can be divided into two main types: i.e. those that keep the species alive by controlling the reproductive systems of both sexes, they are called sex hormones (androgens, estrogens and progestogens), and those that keep the individual alive by helping to regulate the metabolism, they are called adrenocortical hormones (mineralo- and gluco-corticoids). The road from the first discovery of the steroids, via their isolation, their structure elucidation and the synthesis of the sex hormones in the 1930's, to their magnificent application in medicine makes for an extraordinary story.[2]

The total synthesis of steroids remains an active area of research although the aim of the studies and the methods used have changed over the years. The early work in steroid total synthesis served to confirm the structure elucidation of the major steroids: estrone, testosterone and progesterone. After the discovery, in 1949, of the therapeutic importance of the corticoids, a new group of steroids possessing 11-oxygenated functions of which cortisone **1** is the key member, several elegant syntheses were developed with the aim of discovering new routes to these important steroids.



1, cortisone

Examples of such routes are the synthesis of Woodward et al.[3,4] and that of Sarett et al.[5] Although these syntheses reached the pilot plant stage, they proved uneconomical for commercial production. Following the discovery of oral contraception (1959),[6] 19-norsteroids became the object of total synthesis. The Torgov,[7] Smith[8] and Velluz[9,10] syntheses reached the production stage. In recent years, steroid total synthesis has proved particularly useful in demonstrating and

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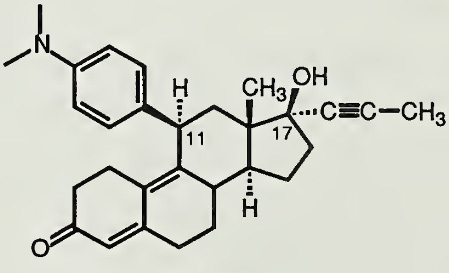
testing new synthetic methodologies and strategies. For this reason, the most significant contributions to steroid total synthesis, precisely steroid hormones, developed by academic research groups will be discussed here[11] in terms of strategy used for the key reaction step, illustrated with some recent examples. Due to the practical use of steroid hormones in medicine and agriculture, the industrial production of physiologically active steroids will also be discussed.[12] Finally, a new application in the field of steroidal antihormones will be reported with the recent availability of mifepristone (RU 486) **2**, a competitive progesterone antagonist offered as a new method for the medical termination of early pregnancy.[13,14]



2, RU 486

ACADEMIC STEROID HORMONE TOTAL SYNTHESES

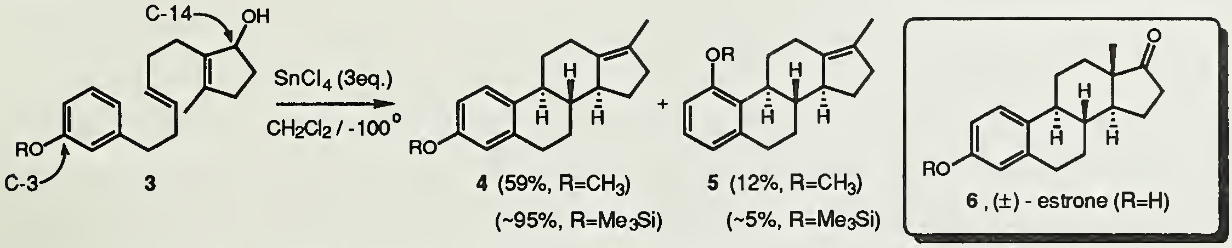
Literature on early steroid total synthesis has been very extensively reviewed.[15,16] Recently, the total synthesis of naturally occuring aromatic steroids (estrone and related 19-norsteroids) was covered by Taub.[17] Finally, a series of books on drug synthesis by Lednicer and Mitscher[18] is regularly updating the work devoted to the steroids, well completed by reviews.[11,19]

Johnson's Biomimetic Cyclizations

In 1955, Stork et al.[20] and Eschenmoser et al.[21] pointed out that the stereochemical course of the biological cyclization of squalene could be rationalized on stereoelectronic grounds. Their important hypothesis immediately stimulated serious biomimetic studies. Since the beginning of his investigations in 1960, W.S. Johnson has shown that certain polyenic substances, having *trans* olefinic bonds in the 1,5 relationship, could be induced to undergo stereospecific, nonenzymic, cationic cyclization to give polycyclic products with the all *trans* ("natural") configuration.[22]

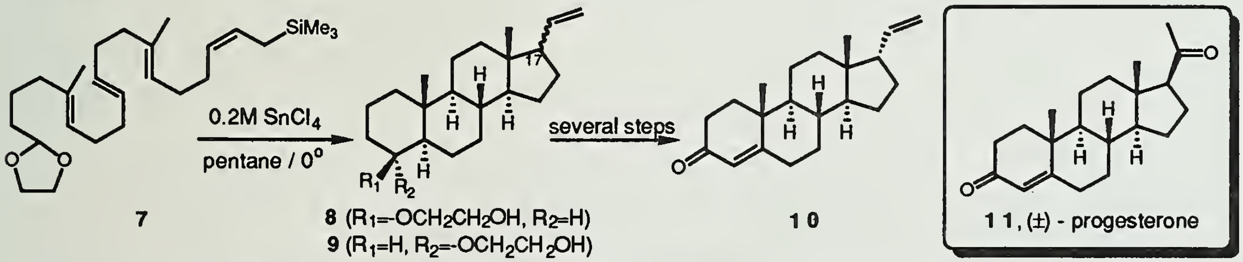
As part of his extensive program on steroid synthesis based on biomimetic polyene cyclization process, W.S. Johnson has developed a stereospecific total synthesis of (±)-estrone known as the Johnson-Bartlett synthesis.[23] Stannic chloride catalyzed cyclization of key intermediate cyclopentenol **3** (R=CH_3) resulted in the rapid formation of the tetracyclic compounds **4** and **5** (R=CH_3) in the ratio of 4.3:1. The para:ortho isomer ratio and the rate of cyclization were found to be dependent on the nature of the C-3 substituent and the C-14 leaving group. The best results were achieved with the 3-trimethyl-silyl ether of **3**, which gave **4** (R=Me_3Si) and **5** (R=Me_3Si) in the ratio of 20:1 in essentially quantitative yield. Then, subsequent transformations led to (±)-estrone **6** (R=H)(Scheme I).

Scheme I



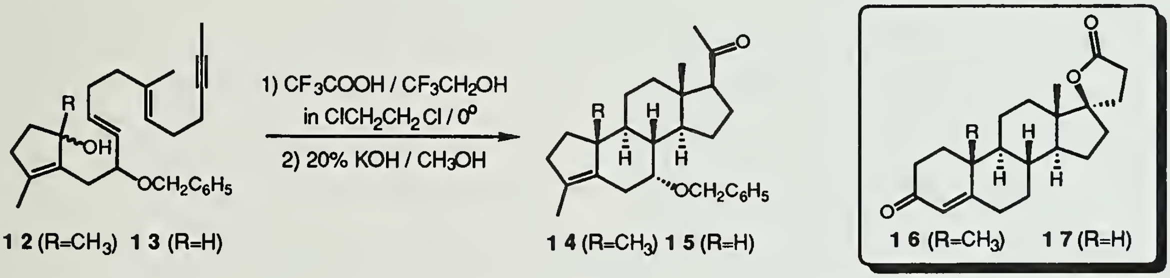
One of the most recent[24] routes to (±)-progesterone developed by Johnson was obtained by formation of the steroid nucleus in one step from an acyclic polyenic chain. Treatment of the acetal **7** with 0.2M stannic chloride afforded as the principal products two pairs of isomers, which proved to be **8** (as a 2:3 mixture of C-17 epimers) and **9** (as a 1:1 mixture of C-17 epimers) in the ratio 2:1. After removal of the hydroxyethoxy side chain followed by an oxidation step, the resulting ketone (as the C-17 epimeric mixture) was submitted to a number of transformations that yielded the unsaturated ketone **10** (17α and 17β forms). After separation by HPLC, a sample of 95% pure 17α-**10** was converted[25] to racemic progesterone **11** (Scheme II).

Scheme II



Finally, an interesting route to optically active steroid hormones was revealed when it was found that the cyclization was stereoselective when a stereogenic center is present at *pro*-C(11).[26] Similar stereoselectivity was also observed when the stereogenic center is at the *pro*-C(7) position.[27a] *dl*-Spironolactone **16** ($R=CH_3$) and *dl*-19-norspironolactone **17** (R=H) were obtained respectively by cyclization of acetylenic substrates **12** and **13** (or their vinylic fluoride analogues) after a series of synthetic transformations (Scheme III).[27b]

Scheme III

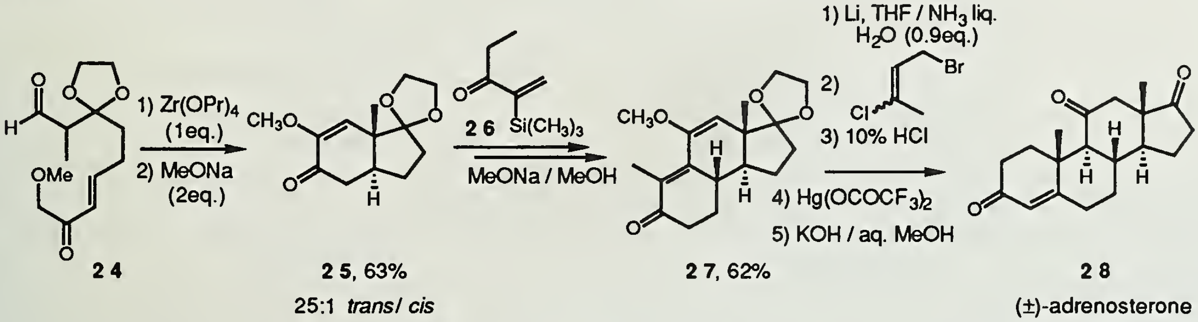


Stork Syntheses

The possibilities of using aldol condensations for steroid hormone total synthesis are illustrated by a short and highly stereoselective synthesis of (±)-adrenosterone by Stork and co-workers.[33]

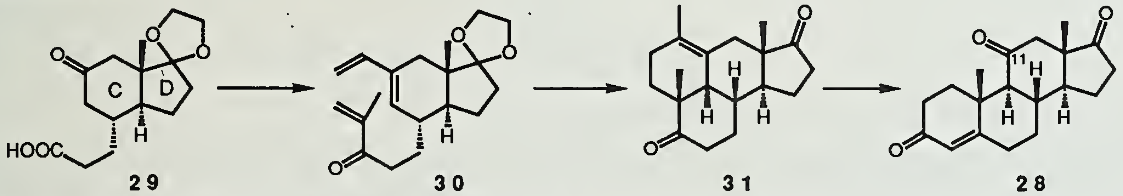
The key intermediate, *trans*-hydrindenone **25**, is obtained by an intramolecular Michael addition of **24** to control the vicinal stereochemistry of the *trans*-fused system. Michael addition of **25** to the less reactive silyl derivative **26** followed by cyclization afforded **27**. Reductive alkylation of the dienone **27** and aldol cyclization then gave (±)-adrenosterone **28** (Scheme VI).

Scheme VI



Another interesting and unusual steroid total synthesis has been reported by Stork and co-workers using a simple internal Diels-Alder sequence of the type shown in Scheme VII for the construction of 11-ketosteroids.[34]

Scheme VII



The key step is the Diels-Alder cyclization of the trienone **30**. Then, the ozonolysis-cyclization sequence yielded adrenosterone **28**. Recently, an enantioselective synthesis of the chiral acid **29** has been reported by Stork.[35]

INDUSTRIAL PRODUCTION OF STEROID HORMONES

The industrial access to steroid hormones constitutes one of the most extraordinary ventures in the history of organic chemistry, due to the fast-developing business of pharmaceutical industry[36] and the diversity of the structures to produce. There are about 500 steroid compounds used at present in therapy, which constitute approximately 10% of the world's total revenue from the production of pharmaceuticals. Steroid drugs producers use three general processes: (1) direct isolation from natural sources, as the recovery of cardiotonic steroids from *Digitalis* and related plants, (2) partial synthesis from relatively inexpensive steroid raw materials[2,37,38] of animal[12] and plant[12,39] origins, and (3) total synthesis[7,8,9f] from non-steroidal materials. All three of these processes are presently commercially operated.

Partial Synthesis Of Steroid Hormones

In the partial synthesis field, steroid hormones are produced by chemical or microbiological transformations[40] of naturally occuring steroid raw materials. Presently, both chemical and microbiological processes are involved in the production of industrial steroids, but bioconversions have preference over chemical means. Compounds with the characteristic steroid structure abound in nature - both in plants and in animals - but concentrations differ widely. For reasons of costs only a few naturally occuring compounds can be considered as starting materials:[41]

Solasodine Tomatidine	*Solanum species*
Smilagenin	*Agave species*
Hecogenin Tigogenine	*Sisal*-plants
Diosgenin	*Dioscorea species*

Sapogenins

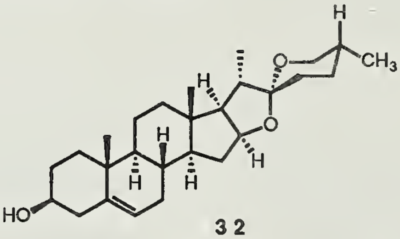
Cholesterol	*Wool-grease*
Deoxycholic acid Cholic acid	*Animal* bile

Animal Sterols

Sitosterol Stigmasterol	*Soy-beans*

Plant Sterols

For decades, diosgenin **32** was undoubtedly the most widely used and most suitable raw material for the production of all steroid hormones.



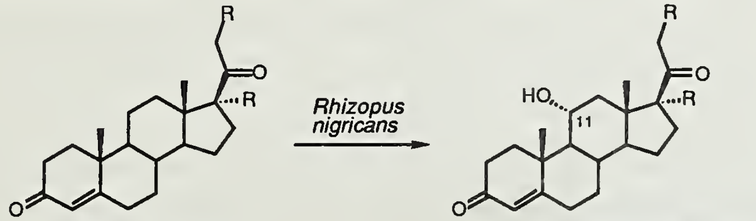
3 2

Diosgenin, a natural substance discovered by R.E. Marker,[39] was found in the roots of several varieties of *Dioscorea*. The main country producing diosgenin is Mexico. In 1976, following the short supply of *Barbasco* (*Dioscorea composita*) and the take over of the gathering of the roots by the State of Mexico, diosgenin reached exorbitant prices. For this reason, the sterols which were available throughout the world gained importance as a raw material. However, the search for new sources of saponins[42] and sapogenins and the exploration of methods for increasing diosgenin production by *Dioscorea* cells in suspension cultures[43] are presently very active.

With regard to the use of bioconversions,[44] there are currently two major biotechnology applications dealing with the steroids[45] or sterols,[46] that of use of microbial agents for processing raw materials into useful intermediates for general steroid production and that of specific transformations of steroid or sterol intermediates to finished products. Of the first, the microbial hydrolysis of plant saponins to sapogenins (dioscin to diosgenin) and the microbial degradation of the side-chain features of sterols are examples of commercial processes.

The first major systematic contributions were reports from the Upjohn Co. that strains of *Mucorales* molds, specifically *Rhizopus arrhizus* (isolated from the air of Kalamazoo, Michigan), were capable of the 11α-hydroxylation[47] of progesterone and cortexolone (Scheme VIII).

Scheme VIII



progesterone (R=H)
cortexolone (R=OH)

11α-hydroxy-progesterone (R=H)
11-epi-hydroxy-cortisone (R=OH)

With the preferred *Rhizopus nigricans*, yields as high as 90% of 11α-hydroxyprogesterone were achieved. One application of bioconversion that continues to be of general interest is the use of microbial agents for specific microbial transformation steps in numerous partial syntheses of steroid hormones. Female hormones (estrone, estradiol, estriol, ethinylestradiol) and corticoids (hydrocortisone, prednisolone) are produced in this manner by pharmaceutical companies.

Presently, there are continuing reports of special process developments, such as use of immobilized cells[48] and enzymes[49], and of searches for microbial steroid esterases, new sterol degradation systems, etc.

Total Synthesis Of Steroid Hormones

At the beginning of 1960's, the development of methods of synthesizing estrone and the 19-norsteroids (contraceptive steroids) led Roussel-UCLAF to the first total synthesis of optically active steroid hormones on the industrial scale.[9a-d]

In 1963, norgestrienone, a component of the oral contraceptive Planor®, was prepared by Roussel-UCLAF.[50] This total synthesis was improved a few years later by incorporation of an enzymatic reduction step with *Rhizopus arrhizus*.[9g]

Schering A.G.[51] used the same bioconversion in its total synthesis of norgestrel, a component of the oral contraceptive Neogynon®, following the Torgov-Smith route.

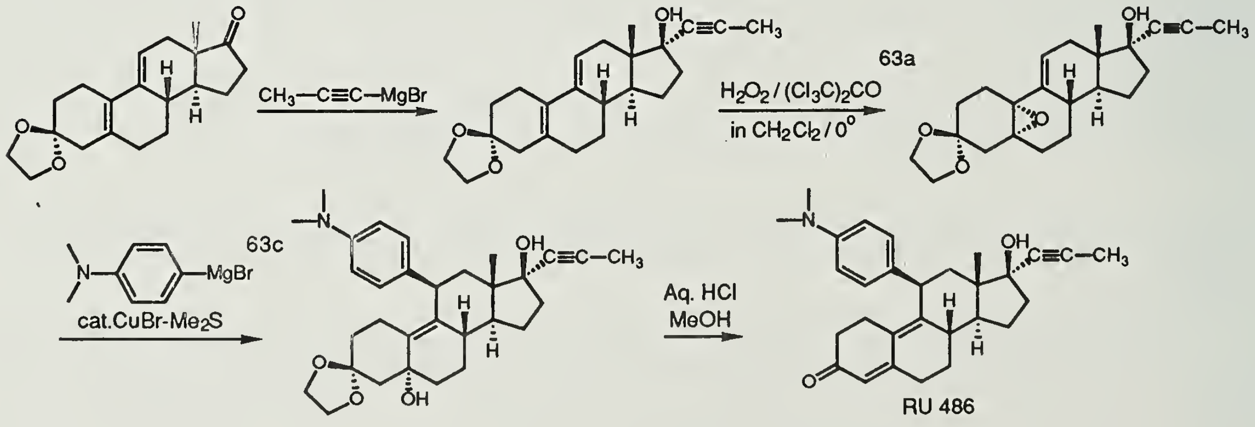
RU 486: AN ANTIPROGESTIN STEROID FOR FERTILITY CONTROL IN WOMEN

Within a few short years since the discovery of the progesterone receptor, chemists have synthesized molecules with a greater affinity for the receptor than progesterone itself and which, while occupying the receptor, fail to trigger the events which transform a target cell from the unstimulated to the stimulated state.[52] Presently, receptor binding is an essential tool in the development and the design[53] of new bioactive steroids.[54] This greater binding affinity is the basis of the competitive inhibitory action of the anti-progestational agent, synthesized by the chemists at Roussel-UCLAF, Paris, and designated RU 486. RU 486 is a compound designed to achieve "contragestion" in women through its antiprogestin activity. Since the report of the potent antiglucocorticoid-antiprogestin activities of RU 486[55,56] and its use as an abortifacient agent in humans,[13,57,58] numerous biological studies have been devoted to this product to elucidate its mechanism of action at the receptor level.[59] Very recently, contragestion with the use of RU 486 in combination with a prostaglandin analogue (gemeprost, Cervagem®)[14,60] has been reported and the drug resulting from this association has been just approved in France and China; no American company appears to have immediate plans to market it in the United States.

Synthesis

The original interest of the Roussel-UCLAF research group in the 11β-substituted 19-norsteroid series was motivated by a general structure-affinity study.[61] As for the synthesis of the novel antiprogestin RU 486, chemistry has unquestionably played a determining role. Prior to the discovery of the original synthetic scheme in 1975 by Roussel-UCLAF chemists, general access to 11β-substituted 19-norsteroids was not available. The finding that unsaturated steroid epoxides react with organocuprates or copper-catalyzed Grignard reagents to produce high yields of the 11β-substituted steroids via conjugate addition opened the road to practically limitless variations.[62] The intermediates, when submitted to hydrolytic ketal cleavage, undergo simultaneous dehydration to the corresponding dienone system. This scheme was applied to the initial synthesis of a selection of 11β-substituted 19-norsteroids, in order to explore their biological potential[61b] and ultimately led to the design of RU 486 (Scheme IX).[63]

Scheme IX



Application

Firstly, RU 486 has been shown to bind to the human progesterone receptor with an affinity approximately identical to that of progesterone itself. Secondly, RU 486 was also found to bind very strongly to the glucocorticosteroid receptor.[64] These two binding properties have given RU 486 to be a strong antiprogestin and a potent antiglucocorticosteroid. As a result of the biological effects, RU 486 is presently used as a medical interruption of early pregnancy (amenorrhea of up to 49 days) with the improvement indicated previously.[14]

CONCLUSION

The synthesis of steroid hormones (or antihormones) is really a subject of current interest at both academic and industrial levels. However, the reasons of interest are quite different. Academic research groups make use of total synthesis to demonstrate and test new synthetic methodologies and strategies. Pharmaceutical industry looks for moneymaking and straightforward routes to produce these bioactive steroids necessary to the needs of modern life. Nevertheless, the tremendous development of bioconversions in the transformation of steroidal raw materials into steroid hormones (or antihormones) must be credited to industry.

Finally, the report of the use of RU 486 as a contragestive reflects the latest advances done in basic biological research in these recent years. The discovery of the fascinating anti-hormonal activities of RU 486 and its analogues is rightly considered a major breakthrough in steroid endocrinology, especially in view of its expected impact on human fertility control. However, this accomplishment raises the question of what are the limits in terms of human race reproduction control.

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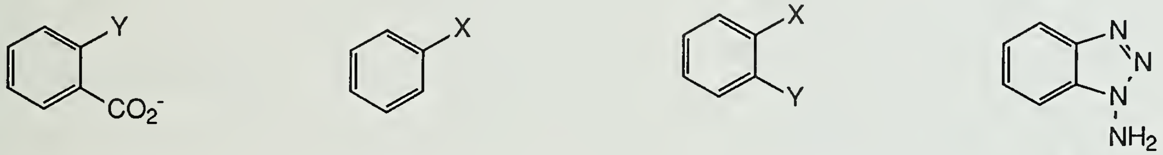
RECENT STUDIES INVOLVING ARYNE INTERMEDIATES

Reported by Kathryn E. Bergmann April 20, 1989

INTRODUCTION

The formation of biphenyls from the reaction of aryl halides with sodium[1] dates back to 1864, but the reactive intermediate benzyne was not known at the time. Eighty years later, nucleophilic addition reactions of aryl lithiums to arynes was pioneered by Wittig,[2] Huisgen, and coworkers; it was a key reaction in the early recognition of benzyne, but the reactive intermediate was looked upon as an unavoidable side reaction. In the past fifty years, the use of benzyne in synthesis has become more prominent, especially in the area of nucleophilic aromatic substitution and the annulation of complex ring systems. Recent studies centered around aryne intermediates will be reported here. Topics will include evidence found in the possible interconversion of benzyne and cyclopentadienylidenecarbene, the regioselectivity and reactivity of substituted arynes, the regioselectivity of tandom aryne addition, and some novel reactions which use aryne intermediates in natural product syntheses.

Benzyne can be generated from several precursors under varying reaction conditions. Thermal decomposition of carbonylate **1** gives benzyne at reaction temperatures above 130 °C.[3] Dehydrohalogenation of **2** can be accomplished by bases such as sodium amide in liquid ammonia, sodium *t*-butoxide, lithium diisopropylamide, and lithium tetramethylpiperidine.[4] 1,2-Dihalobenzenes **3** react with lithium or magnesium by Grignard formation followed by the loss of the metal salt. The mild oxidation of **4** with lead tetraacetate produces benzyne under conditions compatible with many functional groups.[5]



1 $Y = N_2^+$, I^+-Ph

2 X = halogen

3 X, Y = halogen

4

Figure 1

INTERCONVERSION OF BENZYNE AND CARBENE

Mechanistic studies on the possible rearrangement of benzyne, as a high temperature decomposition product of phthalic anhydride **5**, are discussed by Brown[6] and Wentrup.[7]

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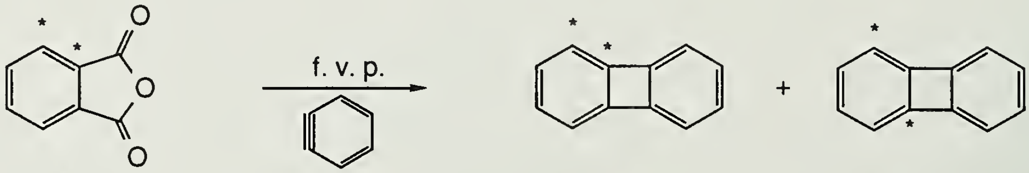
Brown[6a,b] first noticed that flash vacuum pyrolysis (f. v. p.) at 830 °C / 0.1 mm Hg of the anhydride labelled with carbon-14 led to biphenylene products **6** and **7** upon trapping with benzyne generated from unlabelled anhydride (Scheme I). Since the products were formed in equal amounts, he proposed that they came from a common intermediate. Brown assumed that the anhydride decomposed initially to form benzyne which then rearranged to give cyclopentadienylidenecarbene **10** (Scheme II). Carbene insertion in either of two ways leads to carbon scrambling. It should be noted that benzyne is calculated to be 14 kcal/mol more stable than the carbene, and the conversion of the carbene to benzyne would be exothermic.[8]

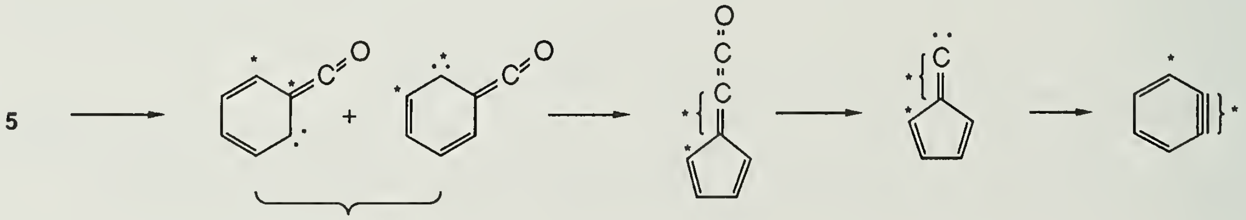
Scheme I



5 **6** **7**

Wentrup[7] pointed out that the initial decomposition product may not be benzyne. His proposed mechanism is shown in Scheme II. The anhydride loses carbon dioxide to form carbene **8**. This intermediate is perfectly suited for a Wolff-type rearrangement to yield cyclopentadienylideneketene **9**. Decarbonylation of **9** leads to cyclopentadienylidenecarbene **10** which may insert to give benzyne. Brown[9] and Hafner[10] previously observed the conversion of carbene **10** to benzyne, but the reverse of this has not been proven. Wentrup isolated the products of the anhydride pyrolysis on KBr windows,[11] and recorded the IR spectra at 77 K, 120 K and 180 K. A broad peak at 2080 cm^{-1} was seen at 77 K and attributed to the triple bond of benzyne. At 120 K, the peak split into a doublet, with maxima at 2090 cm^{-1} and 2080 cm^{-1}. On warming to 180 K, only a single weak absorption was observed at 2080 cm^{-1}. IR absorptions are known to shift to lower frequencies upon warming of the sample.[7] Since benzyne does not survive at 180 K, it is proposed that the absorption observed at 2080 cm^{-1} may be due to the ketene stretch of cyclopentadienylideneketene

Scheme II

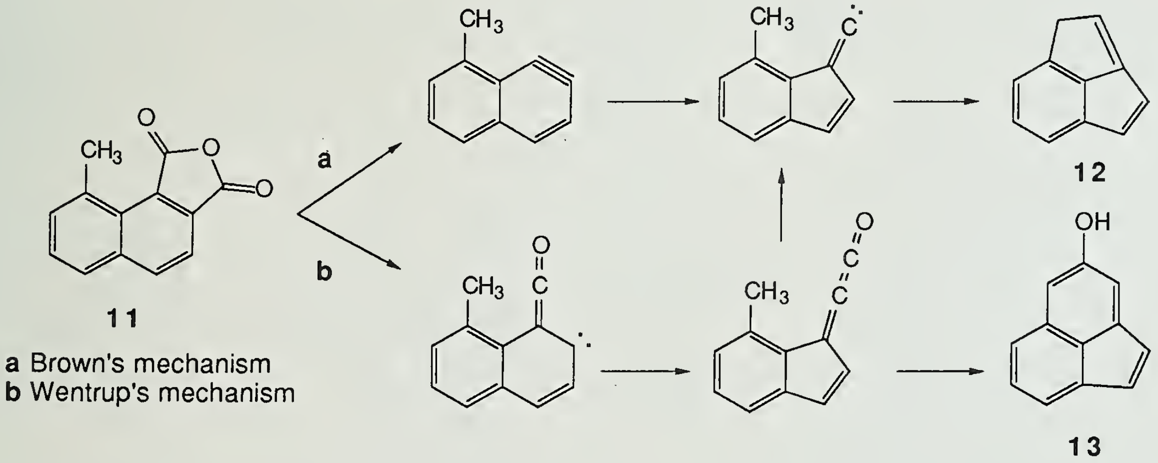


8 **9** **10**

9. This ketene was generated independently and was seen to have an absorption at 2080 cm^{-1}. Since ketene **9** decarbonylats readily at high temperatures thus making it difficult to observe, Wentrup still believes there is insufficient proof of the interconversion of benzyne and cyclopentadienylidenecarbene.

A study by Brown[6c] uncovered evidence against Wentrup's proposed mechanism. Reaction of anhydride **11** (Scheme III) according to the mechanism proposed by Brown would give cyclopentadienylidenecarbene which, in turn, could insert into the carbon-hydrogen bond of the aryl methyl group to form tricyclic cyclopentindene (**12**). If anhydride **11** decomposed by the mechanism proposed by Wentrup, then two products could be formed, the rearrangement product of the ketene to give ancenaphthylen-4-ol **13** and the carbene insertion product to give the tricyclic **12**. Brown synthesized the cyclopentadienylideneketene intermediate from an alternative precursor,[12] and found that under the conditions of pyrolysis the only product formed was ancenaphthylen-4-ol **13**. The anhydride **11** decomposed under the same conditions to give only the carbene insertion product **12**. Therefore the mechanism of decomposition can not be that proposed by Wentrup since no ketene rearrangement was observed.

Scheme III

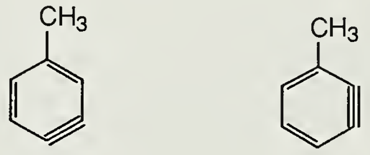


a Brown's mechanism
b Wentrup's mechanism

REGIOSELECTIVITY AND REACTIVITY

Even though reactions involving benzyne are well established, the factors that control regioselectivity of some reactions are still under investigation. Electronic and steric effects on benzyne intermediates have been studied. The choice of aromatic halide, the position and type of substituents relative to the halide, and the number of substituents greatly affect the regioselectivity of the reaction and reactivity of the benzyne intermediate.

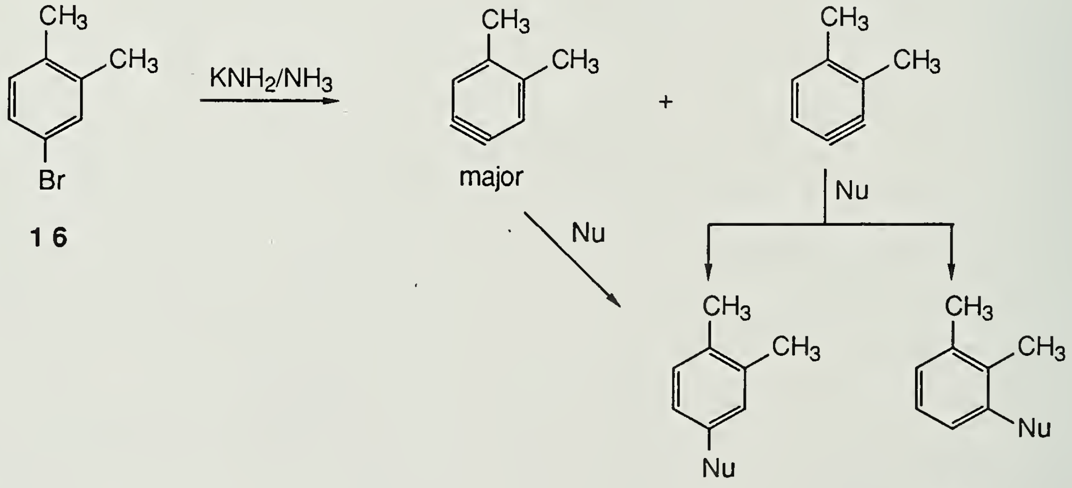
The halide determines the position of the "triple bond." Studies by Biehl[13] showed that the reaction of *m*-bromotoluene favors the 3,4 triple bond **14** whereas the reaction of *m*-chlorotoluene favors the 2,3 triple bond **15** shown in figure 3. The selectivity is only slight due to the weak inductive effect of the methyl group. For example, the regioselectivity of 4-bromo-1,2-dimethoxybenzene (**22**) and 4-bromo-1,2-dimethylbenzene (**16**) is mainly due to the preference of the symmetrical "triple bond" in the 4,5 position (Scheme IV). Reactions with primary amines as the nucleophile give selectivity of 85:15 in favor of the addition product **17** and the selectivity increases to 90:10 for secondary amines, especially when the nucleophiles are large.



14 **15**

Figure 3

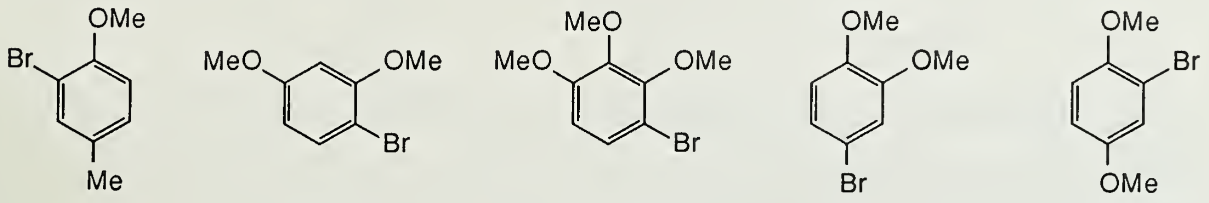
Scheme IV



16 **17** **18**

Methoxy-substituted benzenes are important since many biologically active compounds contain this group. The effects of one, two and three methoxy substituents on nucleophilic addition to benzyne has been studied by Biehl.[14] Monomethoxy-, dimethoxy-, and trimethoxyarenes **19-23** were shown to give cine substitution products in good yield when the benzyne, formed from sodium amide in ammonia, was treated with various amines or acetonitriles; that is the nucleophile attacks the position adjacent to where the halogen had been. As the number of methoxy substituents increase, the yield of the desired substitution product decreases, and the yield of the corresponding aniline increases. Nucleophilic addition with the less reactive but more abundant ammonia solvent is due to the inductive effect of the methoxy substituents which increase the reactivity of the benzyne.

For example, reaction of 4-bromo-1,2-dimethoxybenzene (**22**), where the effect of the methoxy groups is combined,[14] with amines gives predominantly 3,4-dimethoxyaniline. When the methoxy groups are para to one another as in 2-bromo-1,4-dimethoxybenzene **23**, the inductive effects cancel and only the addition of the amine reagent is observed.

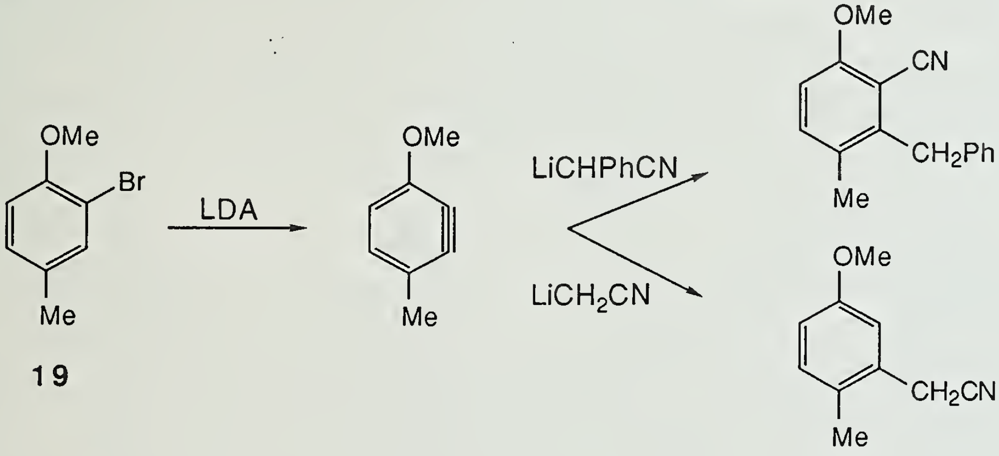


19 **20** **21** **22** **23**

Figure 4

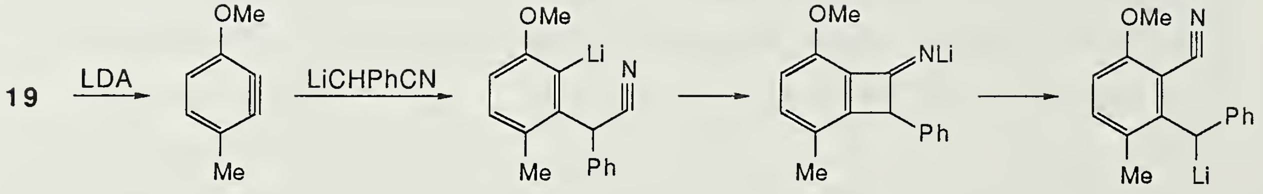
Biehl[15] tried to reduce the amount of aniline side product in these reactions by using lithium diisopropylamide (LDA) as the base instead of sodium amide in liquid ammonia. In the reaction of 2-bromo-3-methylanisole (**19**) with α-lithiophenylacetonitrile under these conditions, the major product was the tetrasubstituted arene **24** in 65% yield (Scheme V). Reaction of **19** with lithioacetonitrile gave only the anion addition product **25**; no rearranged nitriles were detected. Other methyl- and methoxysubstituted 2-bromoanisoles and various aromatic acetonitriles were studied under these conditions. Meta-dimethoxyaryne derived from **20** gave mainly the rearranged product when reacted with α-lithiophenylacetonitrile, whereas the para-dimethoxyaryne[16] derived from **23** gave mainly the anion addition product since the benzyne of **23** is less reactive than that of **20** due to the cancelling of the inductive effects. Scheme VI shows the proposed tandom addition-rearrangement mechanism to account for the rearranged nitrile products. The α-lithiophenyl acetonitrile adds to the position meta to the methoxy substituent. In the cases where the electron-

Scheme V



19

Scheme VI



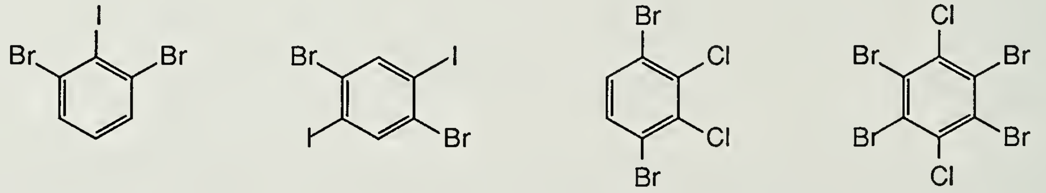
26 **27** **28**

donating substituent on benzyne has a large inductive effect (ortho or para), the nucleophilicity of the position alpha to the methoxy group is increased to such an extent that rearrangement occurs. The resonance stabilization of the arylacetonitriles help stabilize the α-lithio intermediate **28**.

TANDEM ARYNE ADDITION

Many studies have shown that the reaction of polyhaloarenes with Grignards lead to multi aryl-aryl bond formations. The regioselectivity of these reactions depends on the position of the halogens with respect to each other. The mechanism involves aryl Grignard formation followed by loss of the magnesium salt to form benzyne, which then reacts with aryl, vinyl, vinylsilyl,[17] and ethynyl[18] Grignards in good to excellent yields.

The specific arrangement of the halogens on the arene directs the Grignard addition to the subsequently formed aryne. Di-addition can either occur meta[19] from the trihaloarene **29** or para[20] from the dibromo-diiodobenzene **30.** Tri-addition[21] can occur at either positions 1, 2, 3 or 1, 2, 4 from the tetrahaloarene **31**. Even tetra-addition[22] can be accomplished at positions 1, 2, 4, 5 from the hexahaloarene **32**. The reactions give high yields when tetrahydrofuran is used as the solvent with



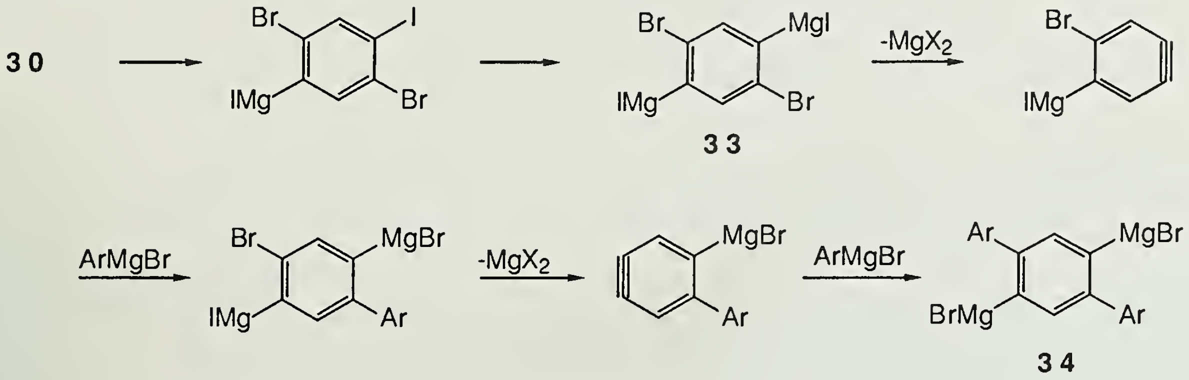
29 **30** **31** **32**

Figure 5

excess Grignard reagent. The regiochemical control for one of these reactions is shown in Scheme VII. Metal-halogen exchange occurs at iodide. The Grignard reagent attacks the subsequently formed benzyne so that the metals are situated para. Addition of the second Grignard reagent occurs regiospecifically so that the metals are once again situated para on the ring to give the di-

Grignard **34**. Various electrophiles can be added to the di-Grignard to produce tetrasubstituted benzenes. Attempts to obtain ortho additions[21] have not been successful due to steric interactions.

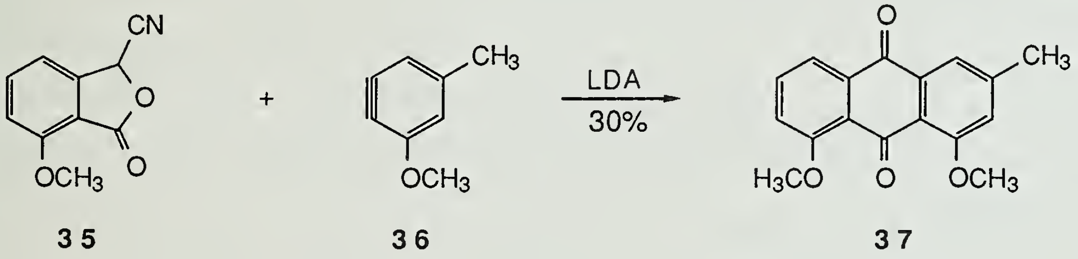
Scheme VII



REACTIONS INVOLVING ARYNE INTERMEDIATES

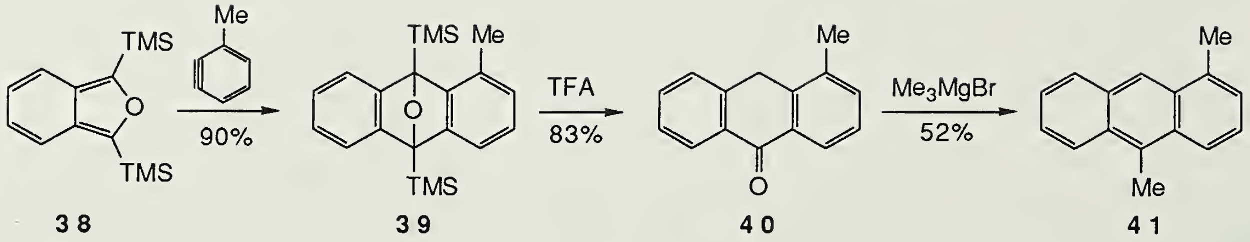
The utilization of aryne intermediates in synthesis is rapidly being explored. A recent study by Biehl[23] on the synthesis of anthraquinones involves nitrile anion addition to arynes. The regioselectivity of the reaction is due to the electron-donating substituent on the aryne, thus directing meta addition of the nitrile anion. In Scheme VIII, 3-cyanophthalide (**35**) reacts with benzyne **36** to produce anthraquinone **37**, the dimethyl ether of the natural product chrysophanol, in 30% yield .

Scheme VIII

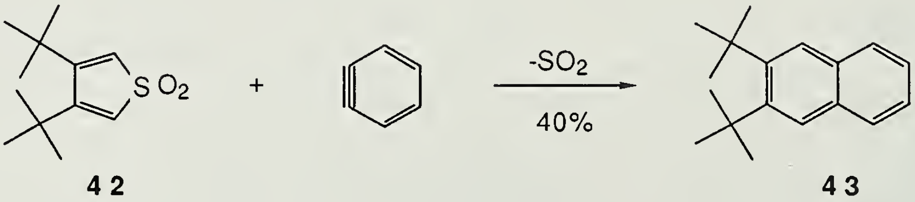


Polycyclic systems can be synthesized by Diels-Alder cycloaddition of arynes with furans. Scheme IX shows an annulation reaction[24] where didehydrofuran **38** is activated by trimethylsilyl groups. The addition product **39** is desilated with trifluoroacetic acid to give anthranone **40** in 83% yield. Treatment of the ketone with excess methyl Grignard gives methylanthracene **41** in 52% yield. 3,4-Di-*tert*-butylthiophene 1,1-dioxide (**42**) reacts with benzyne[25] to give *o*-di-*tert*-butylbenzene (**43**) in 40% yield (Scheme X). The regioselectivity in most cycloadditions is non-existent, but research is being done to improve this.[26]

Scheme IX



Scheme X



CONCLUSION

Two mechanisms have been proposed for the flash vacuum pyrolysis of phthalic anhydride. However, there has not been enough evidence to prove either of them. The conversion of cyclopentadienylidenecarbene to benzyne has been proven, but the reverse has yet to be established. Other studies on the regioselectivity and reactivity of benzyne intermediates show that regiocontrol is dependent upon the position of the functional groups with respect to the aromatic halide. Nucleophilic addition of Grignards to benzyne can produce polysubstituted benzene with good regioselectivity depending upon the position of the aromatic halides. The use of aryne intermediates is becoming more common in the synthesis of natural products since polycyclic systems can be easily synthesized.

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(12) The precursor is a derivative of cyclopentadiene adduct of (*E*)-7'-methyl-1'*H*-indenylideneethanoic acid.

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THE USE OF MECHANISTIC PROBES IN TESTING REACTIONS FOR SINGLE ELECTRON TRANSFER MECHANISMS

Reported by Ingrid Wölfle April 24, 1989

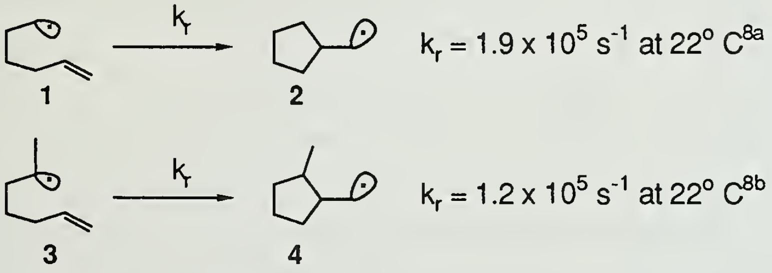
INTRODUCTION

Single electron transfer (SET) has been proposed to be the key step in a variety of organic reactions that were thought to proceed by polar pathways, such as the reaction of alkyl halides with alkyl stannanes[1], organocopper[2] and organolithium[3] reagents, and the reduction of alkyl halides and aromatic ketones with main group metal hydrides[4] and lithium dialkylamides[5].

Single electron transfer reactions can be classified in two major groups[6]: outer sphere (or nonbonded) electron transfer, which results in the formation of free radicals, and inner sphere (or bonded) electron transfer, which is accompanied by the formation of a bond between reductant and oxidant. In the latter case, free radicals are not necessarily formed. Usually, only outer sphere ET has been associated with SET, and it is the observation of radical intermediates or radical derived products that is often taken as evidence for operation of such a pathway.

Several mechanistic probes for the detection of radical intermediates are available.[7] The common feature of these probes is a characteristic rearrangement that they undergo upon conversion to a radical. The most frequently used probes are based on cyclization of the 5-hexenyl (**1**) to the cyclopentylmethyl radical (**2**) (Scheme I).

Scheme I


k_r
1
2
$k_r = 1.9 \times 10^5\ s^{-1}$ at 22° C[8a]
k_r
3
4
$k_r = 1.2 \times 10^5\ s^{-1}$ at 22° C[8b]

For such probes to be useful indicators for the formation of a free radical, their cyclization must occur at a fast enough rate to compete with other reactions, and alternate intermediates such as anions or cations must not undergo the same reaction. Recently, there has been an argument in the literature about how conclusive the observation of rearranged product is.[9] Problems that might arise from the use of mechanistic probes will be discussed.

HYDRIDE REDUCTIONS OF ALKYL HALIDES

The reactions of alkyl halides with metal hydride reducing agents was first examined in 1980 by H. C. Brown.[10] He found their reactivity to decrease in the order I > Br > Cl and 1° > 2°. Thus

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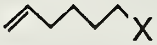
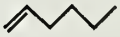
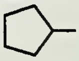
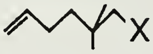
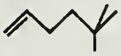
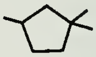
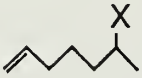
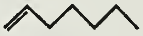
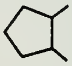
the reduction of primary alkyl iodides with lithium aluminum hydride (LAH) or lithium triethylborohydride (super-H) was complete within a few minutes. These results led him to conclude that the reaction proceeded by an S_N2 pathway.

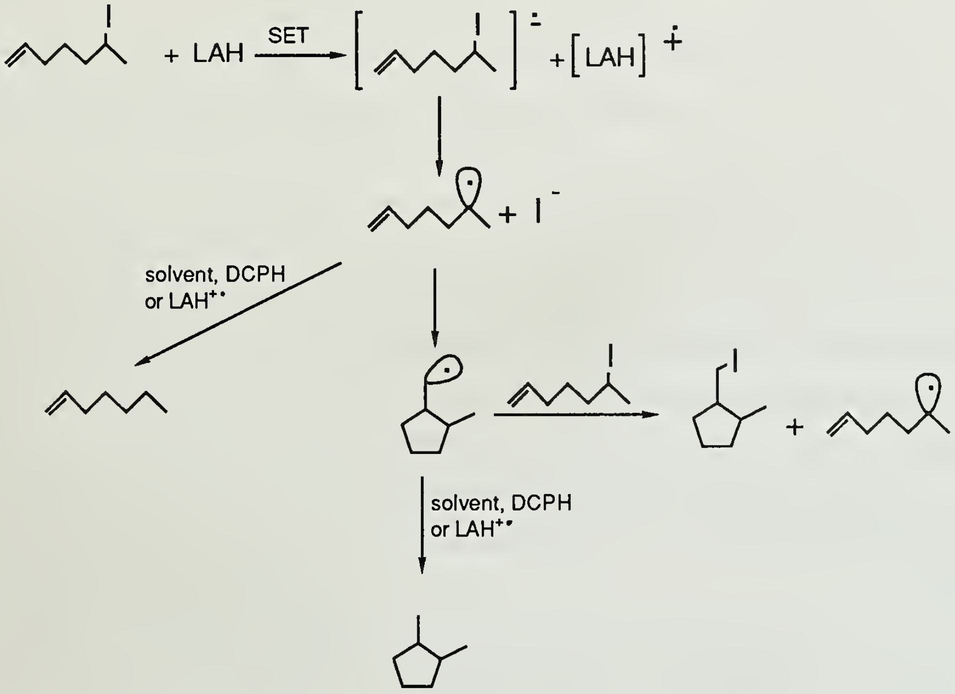
In a parallel study, Ashby and co-workers obtained spectroscopic evidence for radical intermediates in the reaction of LAH with aromatic ketones or hydrocarbons.[11] They were able to detect ketyl radicals and aromatic radical anions by ESR spectroscopy. Consequently, Ashby reinvestigated the alkylhalide reductions, this time using cyclizable probes as the halide substrates.[4a,d] The results of this study are summarized in Table I.

Table I

Halide	Time (h)	% yield (absolute)	
			
X = Cl	168	51	0
Br	24	97	0
I	1	95	0
			
X = OTs	96	1.8	0
Cl	48	0	0
Br	480	9.8	7.5
I	24	3.4	81
I	48	2.5	96
			
X = Cl	48	2.5	0
Br	96	91	2.1
I	4	19	80

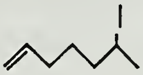
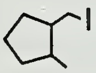
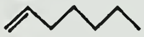
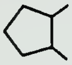
The order of reactivity found by Ashby in these LAH reductions is consistent with Brown's work. Unhindered primary alkyl halides give straight chain hydrocarbon as the only product. Ashby concluded that either the reaction proceeds by an S_N2 mechanism or that hydrogen atom abstraction is faster than cyclization for the 5-hexenyl radical. However, with the more sterically hindered primary and secondary alkyl halides, the situation is different. Whereas chlorides and tosylates react very sluggishly and give only unrearranged product, iodides give mostly cyclized hydrocarbons. Further evidence for the intermediacy of radicals came from trapping experiments in which the probe was reacted with lithium aluminum deuteride (LAD) in the presence of the hydrogen atom donors dicyclohexylphosphine (DCPH) or 1,4-cyclohexadiene (CHD). Unrearranged hydrocarbon (24%) and the cyclized product (19%) were found to have incorporated deuterium. Furthermore, a careful analysis of the reaction mixture showed that in the absence of trapping agent a considerable amount (28%) of cyclized iodide accumulated within one hour. On the basis of these experiments, Ashby proposed an $S_{RN}1$ mechanism for the reduction of hindered iodides by LAH (Scheme II).

Scheme II



Electron transfer from LAH to the halide produces the corresponding radical anion, which readily dissociates to an alkyl radical and a halide ion. The radical can either abstract hydrogen from solvent, the trap, or the LAH radical cation, or it can cyclize. The cyclized radical in turn can either abstract hydrogen from the various sources or it can abstract iodine from the starting halide. Since none of the rates involved were known when this work was done, it was not possible to predict how much of the rearranged product was formed via cyclized iodide. However, Ashby showed that iodine atom transfer must be fairly fast, since he was able to isomerize the probe to the cyclic iodide in 70% yield by treatment with 10 mol% of LAH (Table II).

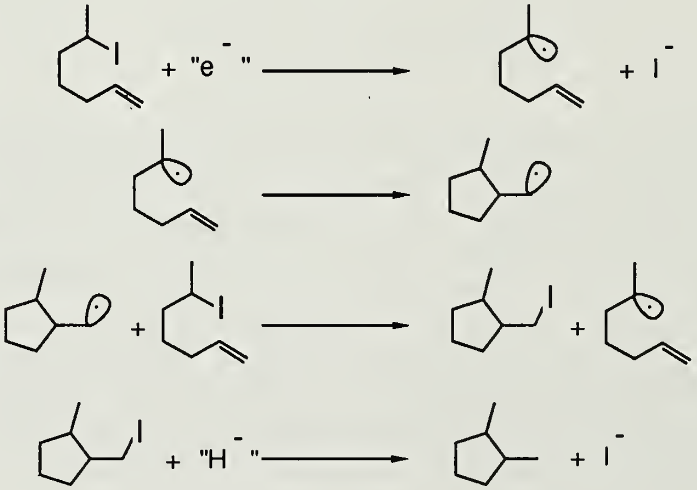
Table II

	% yield (absolute)			
Time (h)				
1	52	38	3.1	3.5
4	26	59	3.2	9.0
70	19	70	2.4	9.4

Although these experiments give no information about how cyclic iodides are converted to product, whether by polar or SET mechanism, Ashby concluded that the main pathway for reduction of hindered iodides by LAH is SET. Only iodides react by SET, he explains, because they are more easily reduced than alkyl bromides or chlorides. However, this does not explain why unhindered primary alkyl iodides give no cyclic product, since their reduction potentials should not be dramatically different.

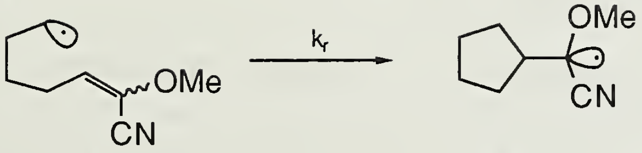
Measurement of the rate constant for halogen atom transfer by Newcomb and co-workers finally clarified the situation.[12] Using two different competition methods, the rate constants for halogen atom transfer to the octyl radical could be obtained. The results show that iodine atom transfer from primary and secondary alkyl iodides occurs with a rate constant of 10^5 M^{-1} s^{-1}, whereas bromine atom transfer is two orders of magnitude slower. Thus halogen atom transfer is always a problem when alkyliodide probes are used, since rate constants for reactions of radicals with LAH[13] and with solvent[14] are only in the order of 10^3 M^{-1} s^{-1}. Newcomb showed that these alkyliodide isomerizations have chain lengths greater than 100. In the case of unhindered primary alkyl iodides the rate of reduction is so fast that probe isomerization does not compete, but it is clear that the more hindered iodides, which are reduced rather slowly, are subject to extensive isomerization (Scheme III).

Scheme III



Newcomb repeated Ashby's experiments using a probe for which iodine atom transfer is endothermic.[15] Whereas cyclization of the 1-cyano-1-methoxyhex(1)en(6)yl radical **5** is more than 100 times faster than the 5-hexenyl radical, the resulting rearranged radical **6** has captodative stabilization (Scheme IV).[16]

Scheme IV



$k_r = 2.5 \times 10^8\ s^{-1}$ at 50° C

5 **6**

It should not take part in the propagation step of the radical chain isomerization. Indeed, no cyclic product was formed when this probe was reacted with LAH or super-H. Newcomb concludes that SET is not an important pathway in these reductions.

METAL-HALOGEN EXCHANGE BETWEEN t-BUTYLLITHIUM AND 5-HEXENYLIODIDES

The mechanism of metal-halogen exchange between organic halides and organolithium reagents is not well understood. Several pathways have been proposed for this reaction, one of which is SET. In 1984, Bailey and coworkers studied the reaction of 6-iodo-1-hexene with t-butyl lithium.[3a] Reaction at -23° C followed by quenching with water gave methylcyclopentane in 85-95% yield. However, Bailey showed that the rearranged product came exclusively from cyclization of hexenyllithium. Variable temperature NMR spectroscopy gave a rate constant for cyclization of 5-hexenyllithium of about $4 \times 10^{-4}\ s^{-1}$ at 0° C.[17]

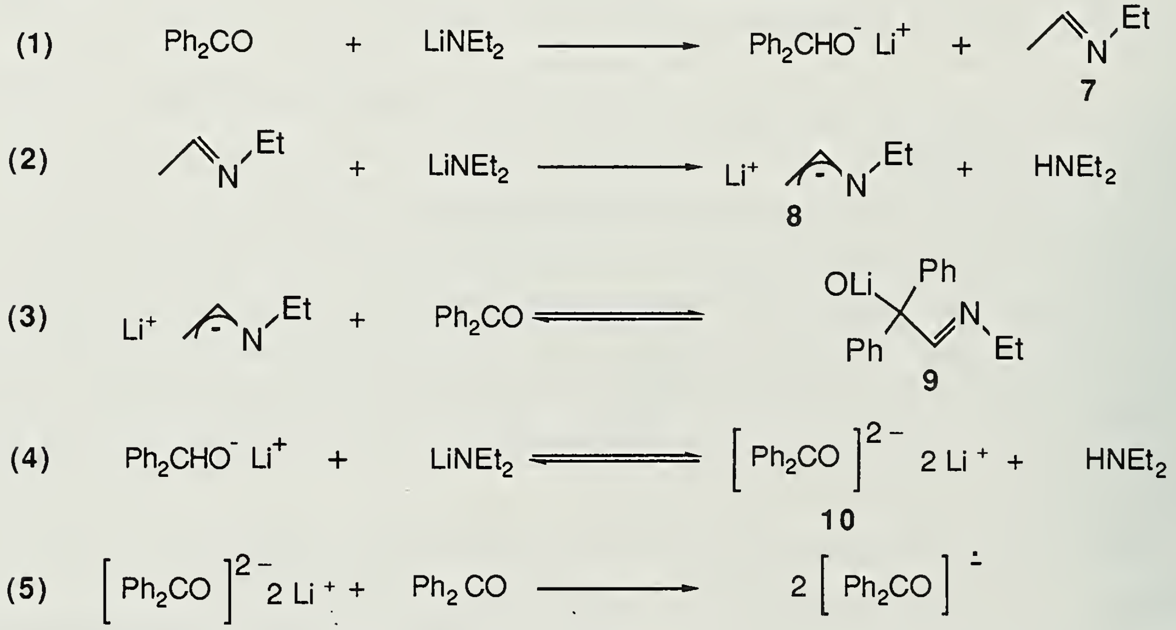
Ashby, who was studying the same reaction, came to a different conclusion.[3c] He found that treatment of 6-iodo-1-hexene with 2 equivalents of t-butyllithium at -130° C gave methylcyclopentane in 19% yield and that the product ratio did not change upon standing at that temperature, indicating that the lithium reagent does not cyclize at -130° C. Like Bailey, Ashby analyzed the reaction mixture after aqueous workup. Bailey later pointed out that water does not quench the lithium reagent at such a low temperature, and that cyclization occured during warmup of the reaction mixture to a temperature where water does quench.[18] Upon addition of methanol to the cold reaction mixture, no cyclized product was detected. Ashby finally agreed that this particular reaction does not proceed by SET.[3d] However, he still claimed that other probes, which do not cyclize by an anionic pathway, give evidence for SET when reacted with t-butyllithium.

THE REACTION OF DIALKYLAMIDES WITH AROMATIC KETONES

The reduction of aromatic ketones by dialkylamide bases has been subject of a number of mechanistic studies. Wittig, who discovered this reaction more than twenty years ago, concluded that it occurs via concerted β-hydride transfer.[19] The observation of pinacol type products by Scott and co-workers was the first indication of an SET pathway for this reaction.[20] Later, Ashby confirmed the formation of ketyl radical by ESR spectroscopy and concluded that the reaction proceeds by an SET mechanism.[5a]

Interestingly, whereas Wittig had noticed that the reaction was complete within one minute at 0°C, Ashby observed that ketyl formation is a very slow process, the maximum concentration of ketyl being observed after eight hours. This apparent contradiction was resolved by Newcomb, who suggested an alternative pathway to ketyl radical (Scheme V).[21]

Scheme V

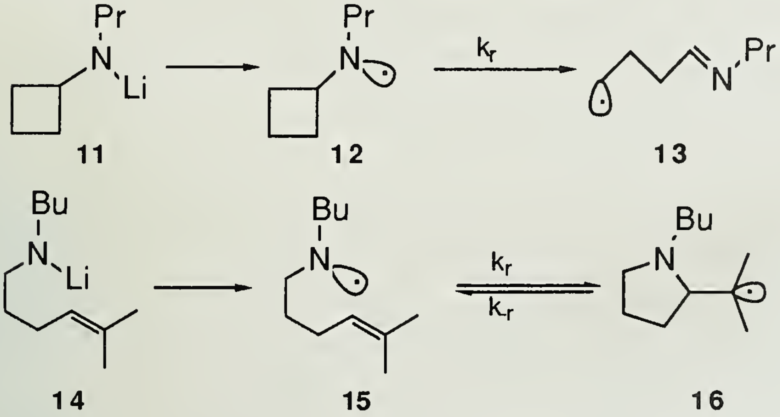


Concerted β-hydride transfer from the amide to ketone gives benzhydrolate anion and the imine **7**. With excess base, this imine can be further deprotonated. The resulting allyllithium anion **8** can reversibly add to benzophenone in competition with initial reduction, thus providing a constant source of benzophenone throughout the reaction. The benzhydrolate formed in step 1 can also be further deprotonated to give a dianion **10**, which then can disproportionate with benzophenone to give two ketyl radicals. Indeed, Wittig had observed that addition of allyllithium **8** to benzophenone competes with β-hydride transfer. He was able to isolate the addition product.

Newcomb's reaction scheme accomodates both Wittig's and Ashby's observations about the rate of reaction. To test this hypothesis further, Newcomb measured the rate of all five steps involved as well as the overall rate of formation of ketyl radical. He found that ketyl formation is indeed kinetically possible by such a pathway. In an experiment designed to imitate the composition of the reaction mixture after initial reduction, he mixed benzhydrol with an excess LDA and added a small amount of addition product **9**. He observed ketyl formation although there was no benzophenone present in the reaction mixture.

Additional evidence for the nature of the reaction mechanism came from a mechanistic probe study.[22] Newcomb argued that if the reduction of benzophenone really proceeds by SET, then aminyl radicals should also be formed. He used two different mechanistic probes for the detection of aminyl radicals, N-lithio-N-propylcyclobutylamine **11** and N-lithio-N-butyl-5-methyl-1-hex-4-eneamine **14** (Scheme VI).

Scheme VI

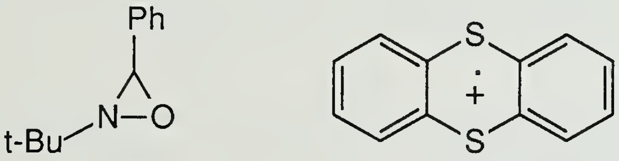


$k_r = 5 \times 10^5\ s^{-1}$ at 50° C[23]

$k_r = 2\text{-}3 \times 10^3\ s^{-1}$ at 50° C[22]
$k_{-r} = 7\text{-}8 \times 10^3\ s^{-1}$ at 50° C[22]

Both probes are stable towards anionic cyclization. The rate constant for ring opening of **12** was available[23], whereas the the rate of cyclization of **15** had to be measured. Unlike its carbon analog, cyclization of **15** is reversible. Using competition methods, both k_r and k_{-r} could be obtained. Despite the fact that ring opening of **16** occurs at a faster rate than its cyclization, amide **14** can be used as mechanistic probe, since the aminyl radical **15** is much less reactive towards hydrogen atom abstraction than the carbon centered radical **16**.

In the reaction of benzophenone with the two probes, no rearranged products were obtained. Furthermore, probe **14** did not cyclize and thus gave no evidence for electron transfer with a variety of other substrates that have been claimed to react with lithium dialkylamides by SET. Examples include dimesitylketone,[5a] anthracene and perylene,[5b] all of which were reported to give spectroscopic evidence for radical intermediates by ESR.



17 18

Figure 1

However, the reaction of both probes with (E)-2-tert-butyl-3-phenyloxaziridine **17** or thianthrene radical cation **18** gave cyclized product, proving that both probes indicate electron transfer when it occurs.

CONCLUSION

As has been shown, the use of mechanistic probes as indicators of electron transfer can be compromised in several ways. Alkyl iodides have been shown to be labile towards isomerization, so that the observation of rearranged products from iodides alone cannot be used as conclusive evidence for SET. Several probes should be employed, preferably those for which isomerization does not occur, i. e. bromides or iodides that give stable rearranged radicals. Also, other pathways to both cyclized products and radical intermediates have to be excluded. Newcomb's study of dialkylamides demonstrates how these probes can be used properly.

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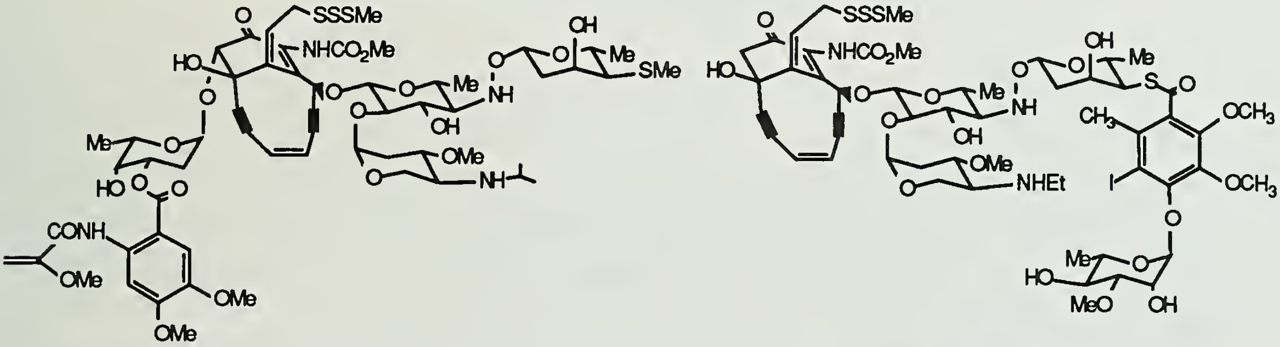
DNA CLEAVAGE:
THE ENEDIYNE SYSTEM OF ESPERAMICIN AND CALICHEMICIN

Reported by Zijian Zeng May 4, 1989

INTRODUCTION

Two novel, naturally occurring compounds with powerful biological properties, esperamicin A1 **1**[1] and calichemicin γ_1 **2**,[2] were recently isolated. Both of them show strong antitumor activity in murine systems. Their structures were determined on the basis of chemical and spectroscopic data and the X-ray crystallographic analysis of partial structures. Remarkably, it was found that esperamicin A1 and the calichemicin γ_1 share a common core-enediyne system, very similar in structure to the neocarzinostatin chromophore (NCS-C),[3] which is a potent DNA cleaving compound.[4]



1: Esperamicin A1 **2**: Calichemicin γ_1

Figure 1

The central core of esperamicin A1 and calichemicin γ_1 contains a number of unusual features: 1) a bicyclo [7.3.1] ring system, 2) an allylic trisulfide attached to the bridging atom, 3) an enediyne system as part of the ring system, and 4) an α,β-unsaturated ketone in which the double bond is at the bridgehead of the bicyclic system. Esperamicin A1 and calichemicin γ_1 also contain several sugars residues attached to the bicyclic system and an aromatic chromophore attached to one of the sugars, as shown in Figure 1.

In this paper, syntheses of model compounds of the core subunit of esperamicin (calichemicin)

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and the DNA cleaving properties of **1** and **2** will be discussed.

STRUCTURE-ACTIVITY RELATIONSHIPS

Structure-activity relationships for both cytotoxicity and DNA cleavage activities in whole cells and *in vitro* have been generated by using structural analogs of espA, including espC, espD, espE, espZ, and espX (esp = esperamicin).[5] These analogs were prepared by chemical hydrolysis of espA. EspC, espD and espE contain the intact central cores with varying numbers of sugar residues, while the central core in espZ and espX has undergone reductive cyclization of the trisulfide and subsequent aromatization of the enediyne structure.

Table I. Cytotoxicity analysis of esperamicin analogs in eukaryotic cells

			IC_{50}, *u* g/ml		
Analog	B16-F10	HCT116	H2981	MOSER	SW900
espA	0.0045	0.0003	0.0018	0.0083	0.0022
espC	0.85	0.067	0.71	1.5	1.04
espD	4.6	0.87	2.7	>12	4.9

espE, espX, and espZ were not cytotoxic at 12 μ g/ml.

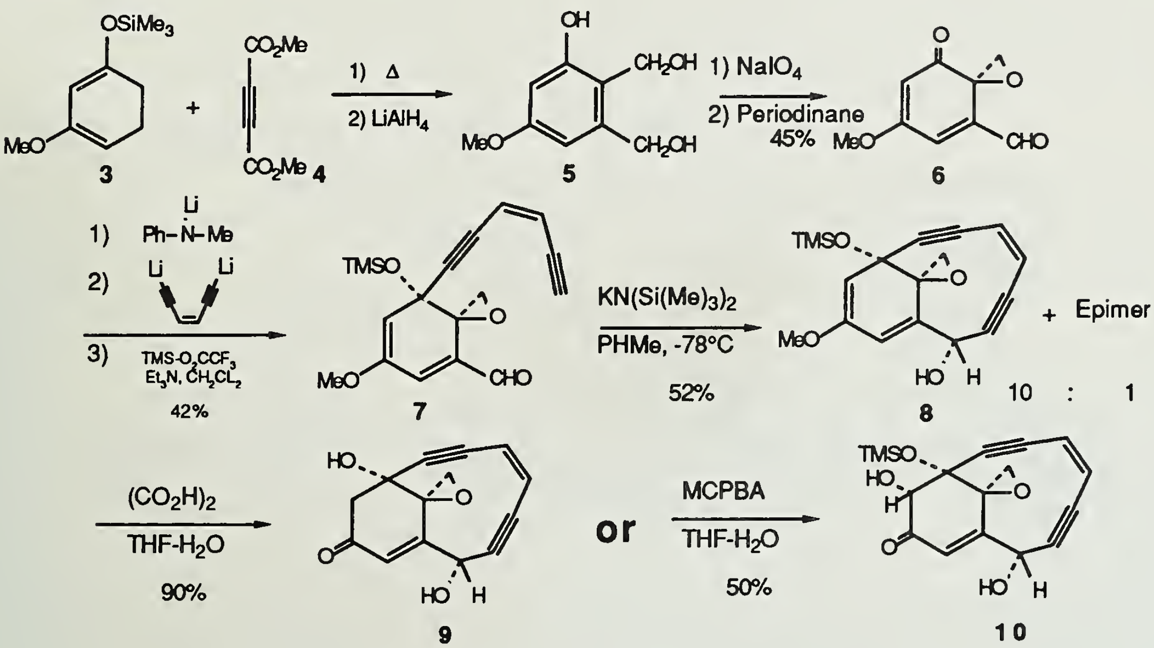
The assays for eukaryotic cytotoxicity confirmed that espA is an extremely potent antitumor antibiotic (Table I). The espA analogs were considerably less potent, with espE, espX, and espZ showing no cytotoxicity at concentrations up to 12.5 μg/ml. EspC was approximately 1/200th as potent and espD was approximately 1/1000th as potent as espA. The potencies relative to espA for DNA cleavage in intact cells are approximately 1/200 for espC, 1/3000 for espD, 1/100000 for espE, and 1/20000 for espZ.

These data suggest that two structural features of the molecule are essential for its biological activity: namely the enediyne group and the intact trisaccharide. EspA and espC both displayed equal potencies in the bacterial DNA repair assay and in the *in vitro* DNA cleavage assay. Yet they displayed different potencies in the eukaryotic cytotoxicity assays, and in the intact cell DNA cleavage assays. Partial loss of sugars from the trisaccharide (espD and espE) resulted in a dramatic loss in activity. These results suggest that the trisaccharide is necessary for activity whereas the deoxyfucose-anthranilate group only affects drug accumulation in intact cell. Most important is the enediyne group, which is an essential funtional group for its biological activity, as shown by the lack of activity for espX and espZ.

SYNTHESIS OF THE CORE SUBUNIT

The unusual enediyne structure of esperamicin and calichemicin has intrigued synthetic organic chemists. Several approaches have been taken to synthesize the core subunit.[6] All of them concentrated on how to prepare the enediyne system and on how to effect the macrocyclization. Two representive syntheses are given by Danishefsky[7] and Magnus.[8]

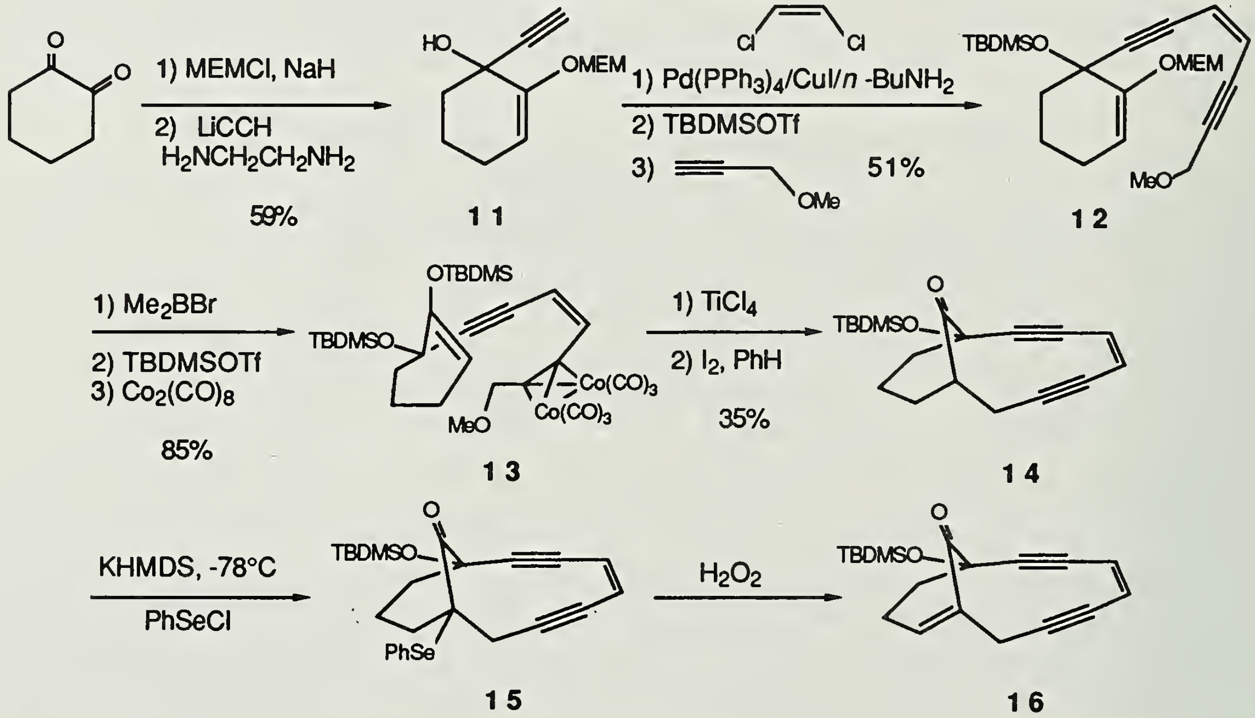
Scheme I



Danishefsky's synthesis began with diene 3 (Scheme I). The six membered ring in the core subunit was prepared by a Diels-Alder reaction to afford 5. The spiroepoxide 6 was introduced as a possible precursor to the allyl trisulfide through the chemistry of Alder and Becker.[9] Selective addition of 1,6-dilithio-1,5-hexa-3-enediylide to ketone 6 was achieved by *in situ* aldehyde protection[10] with lithio N-methylanilide. The bicyclic system was formed by deprotonation of the alkyne of compound 7 with hexamethyldisilazide followed by closure on the aldehyde. In order to prepare compound 9, which is a highly functionalized version of calichemicin, the bicyclo compound 8 was hydrolyzed under acidic conditions. When 8 was treated with mCPBA, the siloxyketone 10 was obtained. Compound 10 contains the additional oxygen required for esperamicin, though an inversion at carbon 10 would be required. The stereochemical assignments of 9 and 10 have been confirmed by X-ray analysis.

In another synthetic effort, Magnus employed the Castro-Stephans cross coupling reaction between ethylene and acetylene to prepare the enediyne system (Scheme II). Starting from 1,2-cyclohexanedione, alcohol 11 was obtained by addition of the lithium acetylide ethylenediamine complex to the monoprotected ketone. Two consecutive coupling reactions afforded enediyne 12. The terminal acetylene group was masked by formation of the cobalt complex 13, and the ring closure was achieved by electrophilic addition of the cation generated by $TiCl_4$. After release of the cobalt and cyclization, a selenoxide elimination was utilized to produce the bridgehead double bond. Compound **16** has the carbon skeleton of esperamicins and calichemicins, but functionalization of C-8 and C-13 are needed to finish the synthesis of the core subunit.

Scheme II



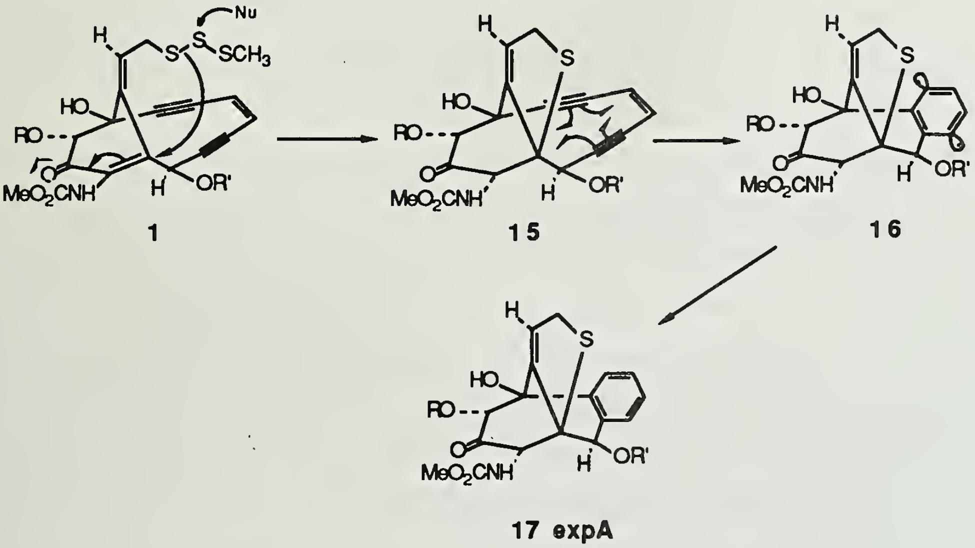
In general, Danishefsky's synthesis involves the introduction of the enediyne as one unit followed by the cyclization of the enediyne with the aldehyde. In Magnus's synthesis, the enediyne was introduced stepwise and the electrophlic addition of cation to the double bond accomplished the macrocyclization. Synthesis of model compounds not only can generate less complex variants which might mimic the DNA cleaving ability of the drug, but also may help to elucidate the DNA cleavage mechanism of **1** and **2.**

DNA CLEAVAGE MECHANISM

The structure of espX (**17**),[11] an analog of espA, was determined by X-ray crystallographic analysis. The structure of espX not only sheds light on the structure of espA but also provides insight into the probable mechanism of action of these compounds. In esperamicin X, the structural features of the esperamicins were present with the following exceptions: 1) the α,β-

unsaturated ketone was replaced by a saturated ketone with simultaneous saturation of the C9-C10 double bond; 2) the fragment of CH_3S_2 was eliminated; 3) the enediyne function was replaced by a 1,2-disubstituted benzene ring. From these changes in structure, a hypothesis for the mechanism of DNA cleavage was proposed: First, bioreductive cleavage of the allylic trisulfide occurs to generate a thiolate followed by a Michael addition into the bridgehead olefin. This facilitates coupling of the enediyne to form a phenylene diradical (Bergman reaction[12]). DNA damage can then result via a hydrogen atom abstraction from the phosphate backbone (Scheme III).[1] The DNA cleavage by NCS-C is also believed to involve a diradical.[4]

Scheme III

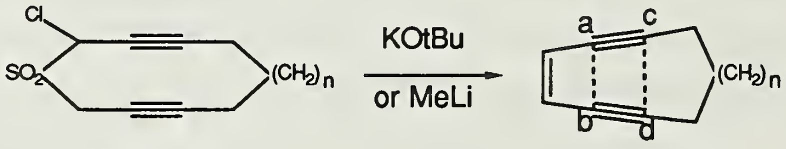


The geometric requirement

In the proposed DNA cleavage mechanism, it was hypothesized that the existence of the bridgehead double bond prevented the termini of the diyne from approaching one another closely enough for cyclization to occur. The saturation of the bridgehead double bond after the conjugate addition may result in shortening of the distances between the acetylenic groups (Scheme IV, distances a-b and c-d).

In order to test the geometric requirement for cyclization, a series of compounds which contain conjugated enediynes were synthesized by Nicolaou[13] according to the general strategy outlined in Scheme IV. Inspection of the calculated strain energies, the distance between acetylenic carbons and the thermal stabilities leads to the following conclusions: the turning point from stability to spontaneous cyclization is apparently in the c-d range of 3.20-3.31 Å. Compounds with a c-d value smaller than 3.20 Å have been claimed as transient intermediates, cyclizing spontaneously to a benzenoid system.[14] The calculated c-d value for **1** is 3.35 Å and the compound is stable at 25 °C, while the intermediate **15** has a c-d value of 3.16 Å, indicating that it should cyclize spontaneously. In order to test the reliability of the calculated c-d values, an X-ray crystallographic analysis was carried out for the 11-membered enediyne **20** (n=3).[13] The agreement of the experimentaly derived values with those obtained by calculation is remarkable (for **20** (n=3), the calculated c-d is 3.61 Å, the experimental c-d is 3.66 Å).

Scheme IV



19 (n = 2-8) **20** (n = 2-8)

Nicolaou[13] noticed that the parent 10-membered ring system **20** (n=2), which has a c-d distance of 3.25 Å falls in the middle of the critical range (3.20-3.31 Å) and the estimated activation energy for the transformation **25**→ **26** is 23.6 kcal/mol. Based on these results, the conjugated cyclodecaenediyne diol **25** was designed as a DNA-cleaving molecule. It was expected that this compound would be stable at ambient temperatures but that it would undergo Bergman cyclization when the temperature was raised above 37 °C.

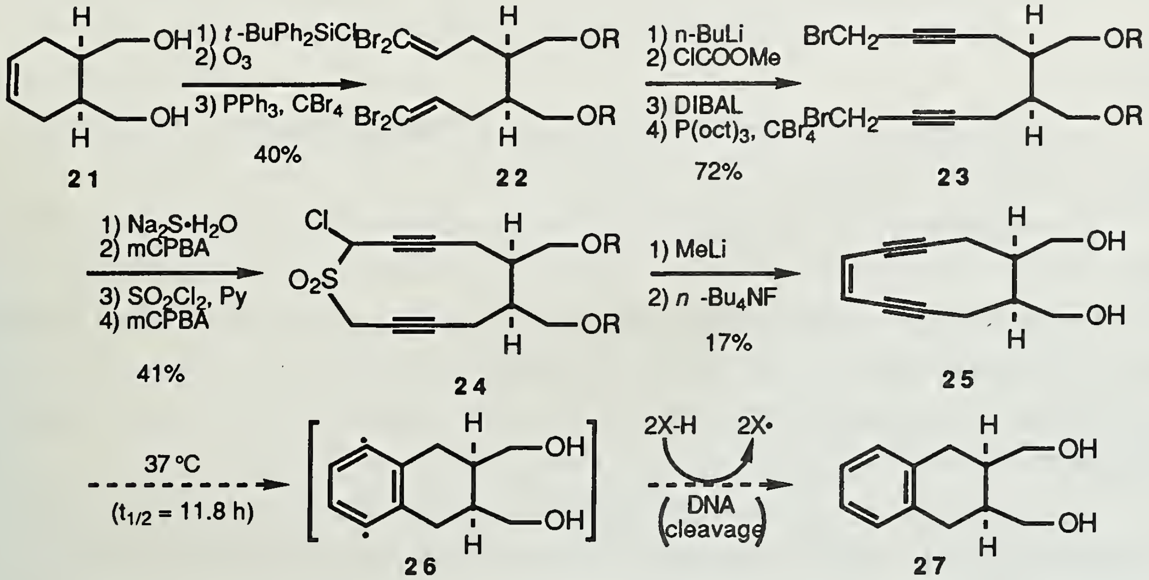
Starting with diol **21** and following their general strategy for the construction of cyclic conjugated enediynes, the proposed compound was synthesized as summarized in Scheme V.[15] This compound was sufficiently stable for isolation and handling at ambient temperature. However, it cyclized at 37 °C with a half life of 11.8 h leading to compound **27** via the presumed diradical **26**, heightening the expectation for **25** to show DNA-cleaving properties. Thus, incubation of **25** with øX174 Form I DNA aerobically produced clean Form II DNA and finally Form III DNA as shown by gel electrophoresis analysis. As expected, incubation of **27** with DNA did not cause any cleavage. These results support the proposed mechanism of action of the calichemicins and the esperamicins.

DNA binding mode

The study of structure-activity relationships for esperamicin clearly show that the enediyne and the trisaccharide are responsible for its biological activity. Although no similar study has been done with calichemicin, it is reasonable to assume that the same functionalities are responsible for its activity.

The DNA cleavage study of calichemicin by Zein *et al* .[16] shows that calichemicin interacts with double-helical DNA in the minor groove and causes site-specific double-stranded cleavage.

Scheme V



In order to understand all these biological phenomena from a molecular level, a DNA binding model was presented by Schreiber.[17] Docking experiments with computer generated models of calichemicin and a dodecamer duplex which served as a calichemicin cleavage site were performed. The results show that with the polysaccharide wound along the minor groove of DNA, the enediyne group was parallel to the axis of DNA and served as a cleaving function toward duplex DNA.

CONCLUSION

In conclusion, the biological properties of esperamicin and calichemicin are not well known. However, the synthetic efforts directed toward the core subunit were quite successful. The detail of DNA cleavage mechanism, such as DNA binding mode and DNA cleaving pathway, is still under investigation.

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CATALYTIC ANTIBODIES:
AN APPROACH TO ARTIFICIAL ENZYMES

Reported by Weiming Wu May 11, 1989

INTRODUCTION

Antibodies are proteins synthesized by an animal in response to the presence of a foreign substance. These soluble proteins are the recognition elements of the *humoral immune response.* Each antibody has specific affinity for the substance that stimulated its synthesis. The ligand-binding sites of antibodies have enzyme-like affinities and specificities. The fact that large amounts of monoclonal antibodies can be generated for most biologically active macromolecules as well as small synthetic molecules[1] has made antibodies one of the most important classes of receptors in biology and medicine. The recent development of strategies for introducing catalytic activity into antibodies and the potential of providing general routes for the construction of enzymatic catalysts with tailored specificities will be discussed in this abstract.

A basic principle of enzyme catalysis states that strong binding interactions between the enzyme and transition state are required to reduce the energy barrier along the chemical reaction pathway.[2,3] This was firmly established by the fact that substances which mimic the structure of a transition state in a particular enzymatic reaction are bound tightly to enzymes involved in the reaction and act as enzyme inhibitors.[4] It is reasonable to propose that a receptor designed to optimally bind a transition state would achieve the catalytic function of an enzyme. The demonstration of this would reinforce the principle of enzyme active site-transition state complementarity and open a powerful approach to devising artificial enzymes.

Monoclonal antibodies, elicited to transition state analogs of chemical reactions, should behave as enzymatic catalysts to the corresponding reactions. The generation of monoclonal antibodies is attributed to the discovery by Milstein and Köhler[5] that large amounts of homogenous antibodies of nearly any desired specifity can be obtained by fusing an antibody-producing cell with a myeloma cell. Most small foreign molecules (called *haptens*) do not stimulate antibody formation, however, they can elicit the formation of specific antibodies if they are attached to macromolecules such as proteins, polysaccharides, or nucleic acids. For example, the transition state analogs discussed in this paper are coupled to the carrier proteins bovine serum albumin (BSA) or keyhole limpet hemocyanin (KLH).[6]

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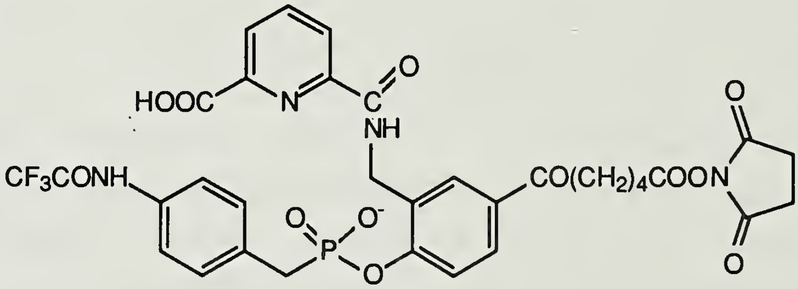
ACYL-TRANSFER REACTIONS CATALYZED BY ANTIBODIES

The catalytic properties of antibodies specific to transition state analogs for the hydrolysis of esters and carbonates were investigated first. These well-characterized reactions were chosen in order to simplify mechanistic studies of ligand binding and catalysis and because tetrahedral phosphonates and phosphonamidates have been reported to act as transition state analog inhibitors for enzymatic peptide hydrolysis.[7]

Hydrolysis of Esters

In 1986, Tramontano[8] first studied the specific hydrolysis of the coumarin ester of *p*-trifluoroacetamidophenylacetic acid. The antibody elicited to the transition state analog phosphonate **1** was found to catalyze the hydrolysis of ester **2a** with kinetics consistent with the Michaelis-Menten rate expression. The values for the catalytic constant, k_{cat}, and the Michaelis constant, K_m, were found to be 1.3×10^{-2} sec^{-1} and 1.25 μM, respectively. Comparing the apparent second-order rate constant k_{cat}/K_m of 1.04×10^4 M^{-1}•sec^{-1} with the second-order rate constant of the imidazole-catalyzed hydrolysis of **2a** (0.346 M^{-1}•sec^{-1}) showed a rate increase of 3×10^4.[8a] The phosphonate **1** was a potent inhibitor of hydrolysis, which was reflected in the value of the inhibition constant K_i = 35 nM.



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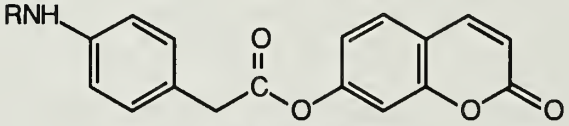


2a R = CF_3CO
2b R = CH_3CO

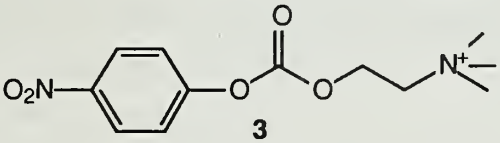
Activity was found to be specific for hydrolysis of the ester possesing the trifluoroacetamide substituent which was present in the phosphonate structure. Ester **2b** can be hydrolyzed under normal condition as easily as ester **2a**, but the slight difference in structure did not allow it to react with this antibody.

The pH dependence of the hydrolysis rate was studied and it was found that the V_{max} increased with increasing pH while the K_m remained constant. The involvement of a nuleophile in the binding site was also investigated by the effect of protein modification reagents on hydrolytic activity. The alkylation of cysteine in the protein with iodoacetamide had no influence on activity.[8a] Acylation of surface lysine and amino-terminal peptides by exhaustive treatment with N-succinimidylpropionate reduced activity by 75%.[8a] Nitration of tyrosine by tetranitromethane[9] reduced activity by 60%.[8a] Diethyl pyrocarbonate, a histidine-specific reagent,[10] destroyed all activity at a reagent/ protein ratio of less than 10:1.[8a]

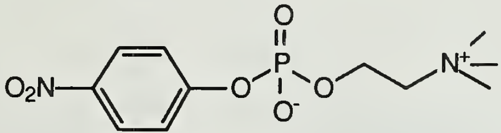
When the reaction product was exposed to alkaline buffer or hydroxylamine, the activity of the antibody was recovered. This is similar to the behavior of enzymes like chymotrypsin,[11] which form covalently bound intermediates by a nucleophilic transacylation process. The pH dependence of the rate constant (k_{cat}/K_m) may imply the ionization of an active site nucleophile in the antibody. The dramatic effect of histidine modification suggests that the imidazole group is participating in the transacylation reaction and may act as a nucleophilic or general base catalyst in the acylation of tyrosine, for example. The effect of lysine modification may result from structural changes in the antibody that change the binding properties.[8a]

Antibody Binding Sites Studies

The aqueous hydrolysis of carbonate **3** and the structure of catalytic antibodies was studied by Schultz.[12] Antibody MOPC167 tightly binds *p*-nitrophenylphosphorylcholine (**4**), a transition state analog for the hydrolysis of carbonate **3**. Antibody MOPC167 is a member of a well-characterized class of antibodies specific for phosphorylcholine (PC) ester.



3



4

The X-ray structure of antibody McPC603, which is highly homologous to antibody MOPC167, has been solved.[13a] The tetrahedral phosphate in the McPC603-PC complex is stablized by hydrogen bonding and electrostatic interactions with heavy-chain residues Tyr^{33H} and Arg^{52H}, which are invariant in all of the PC-binding antibodies sequenced to date.[13b] This suggests that the binding site of antibody MOPC167 should be complementary to the transition state for hydrolysis of carbonate 3. The positively charged choline moiety is partially neutralized by the conserved heavy-chain residue Glu^{35H}, and the light-chain residue Asp^{97L}. Moreover, the X-ray structure also shows that PC is bound in the cavity of McPC603, with the choline group located deep in the interior and the phosphate group directed toward the exterior, in contact with aqueous solvent. This suggests that the carbonyl group in a MOPC167-substrate complex should be accessible to attack by an external nucleophile such as water or hydroxide ion.[12b]

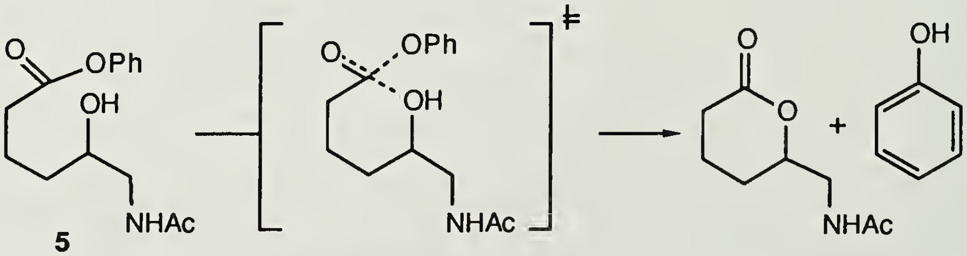
The hydrolysis of carbonate **3** was catalyzed by antibody MOPC167 and was kinetically consistent with the Michaelis-Menten rate expression. The k_{cat} and K_m were found to be 0.40 ± 0.04 min^{-1} and 208 ± 43 μM, respectively. The transition state analog **4** inhibited the hydrolysis of **3** with a K_i of 5.0 ± 1.5 μM. Modification of MOPC167 with tetranitromethane[9] abolished all catalytic actvity,[12b] suggesting the presence of a tyrosine at the catalytic site.

If the role of the antibody binding site is to stablize the transition state formed by attack of an external nucleophile on complexed carbonate **3**, then it would be reasonable to expect a first-order rate dependence on hydroxide ion concentration. The pH dependence of the hydrolysis was examined between pH 6.0 and 8.0. The V_{max} of the hydrolysis exhibited a first-order dependence on hydroxide ion concentration in this pH range.[12b] The role of hydroxide ion may either be to directly hydrolyze the complexed carbonate or to hydrolyze an intermediate covalent choline acyl-antibody adduct.

Stereospecific Lactonization

The intramolecular acyl-transfer reaction has a transition state that may be mimicked by a cyclic phosphonate ester (Scheme I). In the lactonization of δ-hydroxyester **5**, there are two enantiomeric transtion states which would be equal in free energy in the absence of a chiral reagent. But in the presence of antibody they might be unequal in free energy and lead to a stereospecific cyclization.[14]

Scheme I



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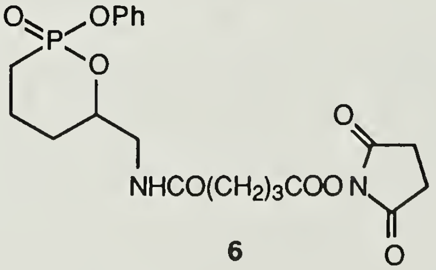


6

Monoclonal antibody 24B11 was elicited to the transition state anolog **6** which was stereospecifically synthesized in four steps.[14] The initial rates in the presence of antibody as a function of substrate concentration followed Michaelis-Menten kinetics, k_{cat} and K_m were found to be 0.5 min^{-1} and 76 μM, respectively. The transition state analog **6** inhibited the reaction with a K_i of 0.25 μM.

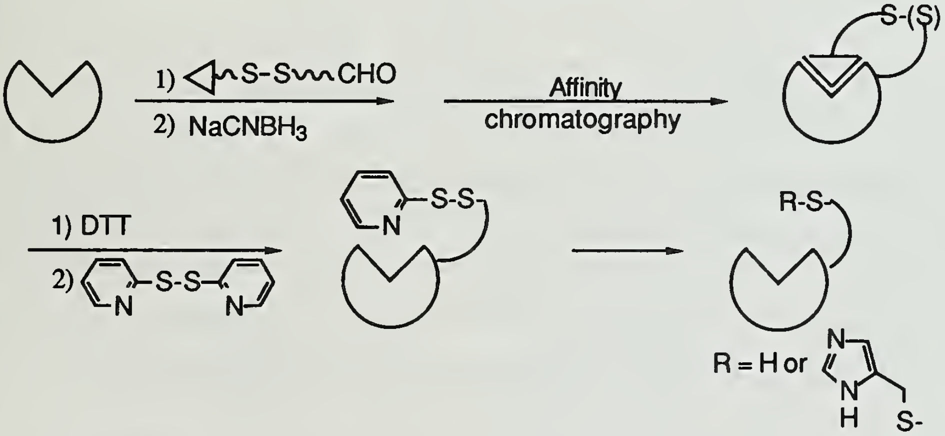
It was found that the reaction ended with consumption of ~50% of the initial ester concentration. Addition of more substrate solution to the reaction solution resulted in a second depletion of ~50% of the freshly added substrate. Introduction of fresh antibody had no effect. The remaining ester was isolated by HPLC and no evidence for cyclization was observed upon addition of fresh antibody. This suggested that the antibody only reacted with one of the enantiomers.

Using ^{1}H NMR spectroscopy in the presence of a chiral lanthanide shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) [Eu(hfc)$_3$], an enantiomeric excess of 94 ± 8% was found for the lactone.

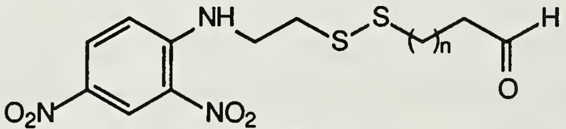
Semisynthetic Catalytic Antibodies

In the previous cases, antibodies were raised against haptenic groups that were designed to generate binding sites with specific catalytic functions, such as stablization of a rate-determining transition state. Alternatively, it should be possible to directly introduce catalytic groups into antibody binding sites by genetic or chemical methods.[15a] In 1988, Schultz developed a chemical strategy whereby antibody binding sites can be selectively modified with a wide variety of synthetic or natural catalytic groups (Scheme II).[15]

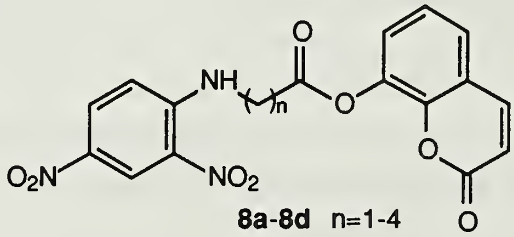
Scheme II



The antibody MOPC315 binds substituted 2,4-dinitrophenyl (DNP) ligands with association constants ranging from 5 x 10^4 to 1 x 10^6 M^{-1}.[16] Cleavable affinity labels **7a** and **7b** were used to introduce nucleophilic groups into the binding site. They consist of the DNP group linked to an electrophilic aldehyde by disulfide linkages which can be easily cleaved. The position of disulfide linkages was designed to approximate that of the ester in the corresponding substrates, in order to insure that the incipient nucleophilic groups were positioned appropriately for attack upon the ester. Only label **7b** was effectively incorporated.



7a n=1
7b n=2



8a-8d n=1-4

It was found that both thiol and imidazole derivatized antibodies can accelerate the cleavage of ester **8b.** The reaction kinetics were consistent with the formation of a Michaelis complex. The reactions were competitively inhibited by N-DNP-glycine (Table I).[15]

Table I Kinetic parameters for catalyzed cleavage of ester **8b**

	k_{cat} (min^{-1})	K_m (μM)	K_i (μM)	$[k_{cat}/K_m]/k_{uncat}$
T	0.87 ± 0.08	1.2 ± 0.1	8 ± 1	6×10^4
I	0.052 ± 0.005	2.2 ± 0.2	4 ± 1	$(1.1 \pm 0.2) \times 10^3$

1) T and I are thiol and imidazole derivatized antibodies, respectively.

The catalytic activity of the imidazole-derivatized antibody showed a pH dependence consistent with a titratable residue with pK_a 7.5 ± 0.3, which is similar to the pK_a (7.5) of 4-methylimidazole.[17] Moreover, the catalytic activity was completely destroyed upon treatment with diethyl pyrocarbonate, an imidazole-specific reagent.[10,15a] These data were consistent with the presence of a catalytic imidazole group acting either as a general base or as a nucleophile in the hydrolysis of ester **8b**.

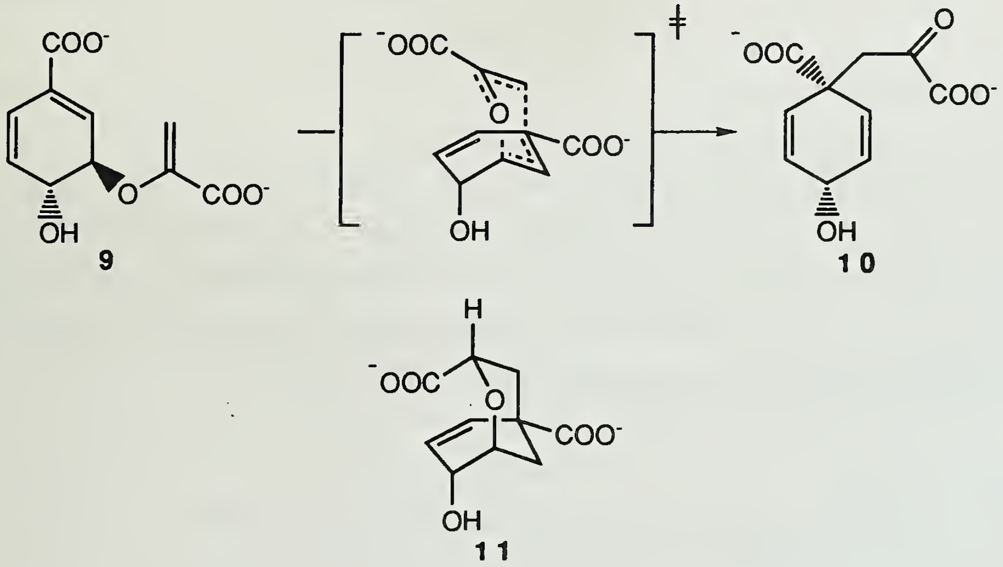
In these cases, the high binding specificity of the immune system can be combined with the diverse and efficient catalytic groups available from synthetic chemistry. In addition, the chemical strategy described here may find applications in the selective modification of other proteins for which the three-dimensional structure is unavailable.

OTHER USES OF CATALYTIC ANTIBODIES

Antibodies have also been induced that are capable of catalyzing the hydrolysis[18a] and formation[18b] of amides. Recently, sequence-specific peptide cleavage catalyzed by an antibody with a metal complex cofactor was reported.[19] Moreover, an acyl-transfer reaction is not the only type of reaction that can be catalyzed by antibodies. It has been reported that antibodies could be exploited in the design of catalysts for pericyclic,[20] photochemical reactions.[21]

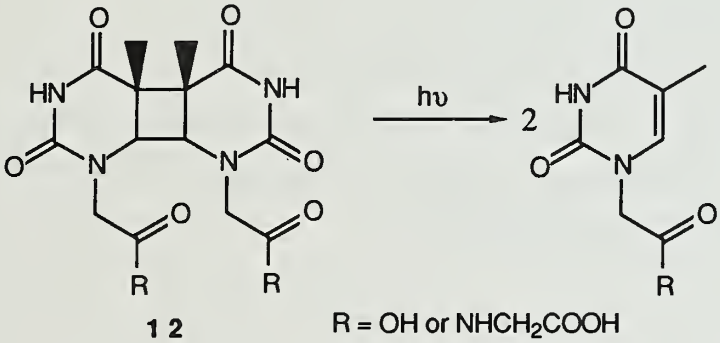
The Claisen rearrangement of chorismate (**9**) to prephenate (**10**) (Scheme III) was found to be catalyzed by the antibody elicited to the transition state analog **11**.[20] Moreover, only (-)-chorismate was a good substrate for the catalytic antibody. The enantioselectivity of the catalyst was shown to be as high as 90:1.[20a]

Scheme III



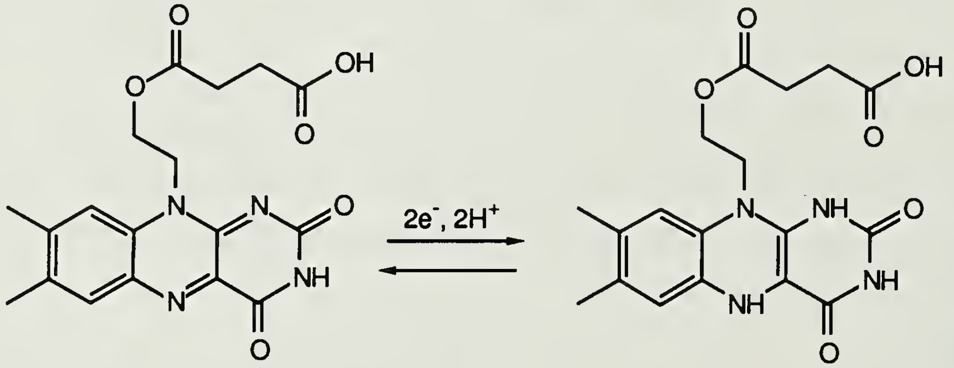
Since antibodies generated against positively charged haptens contain complementary aspartate and glutamate residues, it seemed reasonable that antibodies generated against the polarized π system of a pyrimidine dimer might contain a complementary tryptophan residue in the binding site.[1] It could then act as a sensitizer in the photocleavage of dimer **12** (Scheme IV).[21]

Scheme IV



The differential binding of the oxidized and reduced flavin due to their structural differences was also used to shift the redox potential (Scheme V).[22]

Scheme V



CONCLUSION

It was demonstrated that the high binding specificity of antibodies can be exploited to produce enzyme-like catalysts. Though catalytic antibodies have not been successful so far in providing additional insight into mechanisms of enzyme-catalyzed reactions, they do specifically catalyze chemical reactions by stablizing reaction transition states or by lowering the entropic barriers to reactions. The challenge now is to extend these ideas to the design of catalysts for other reactions of general interest in chemistry, biology, and medicine.

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ORGANIC SEMINAR ABSTRACTS

1989-90, SEMESTER I

University of Illinois

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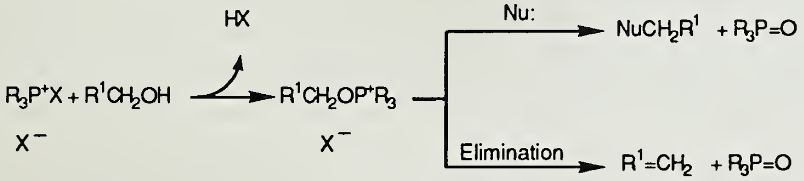
THE MITSUNOBU REACTION: MECHANISM AND APPLICATIONS

Reported by Douglas M. Lucas September 7, 1989

INTRODUCTION

The hydroxyl function does not normally serve as a good leaving group for alcohols. However, alcohols can be activated for loss of the hydroxyl group in substitution and elimination reactions by conversion of the hydroxyl to a good leaving group. A powerful method of hydroxyl activation is the formation of a phosphorus-oxygen bond. The oxygen can then be readily displaced or eliminated with formation of the thermodynamically strong phosphorous-oxygen double bond as shown in equation 1.

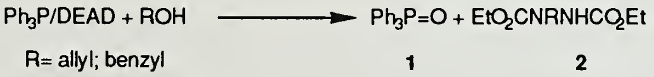


(1)

It has been shown that alcohols treated with triphenylphosphine (Ph_3P) and a dialkylazodicarboxylate give substitution products in the presence of nucleophiles. In the process, the hydroxyl group is clearly activated for displacement. Mitsunobu and co-workers pioneered this work, and they published a review of the use of Ph_3P with diethylazodicarboxylate (DEAD) in synthesis in 1981.[1] Consequently, this method is now commonly referred to as the Mitsunobu reaction. This abstract will deal with the mechanism and recent synthetic applications of the Mitsunobu reaction.

MECHANISM

In 1967, Mitsunobu reported that treatment of allyl or benzyl alcohol with triphenylphosphine (Ph_3P) and diethylazodicarboxylate (DEAD) produced triphenylphosphine oxide (**1**) and diethyl N-alkyl hydrazodicarboxylate **2** as the major products (equation 2).[2] When carboxylic acids were present, the corresponding carboxylic esters and diethyl hydrazodicarboxylate (**3**) were formed as shown in equation 3.[3] Under these conditions in the presence of benzoic acid, the optically active



$$\underset{R = \text{allyl; benzyl}}{Ph_3P/DEAD + ROH} \longrightarrow \underset{\mathbf{1}}{Ph_3P{=}O} + \underset{\mathbf{2}}{EtO_2CNRNHCO_2Et} \qquad (2)$$

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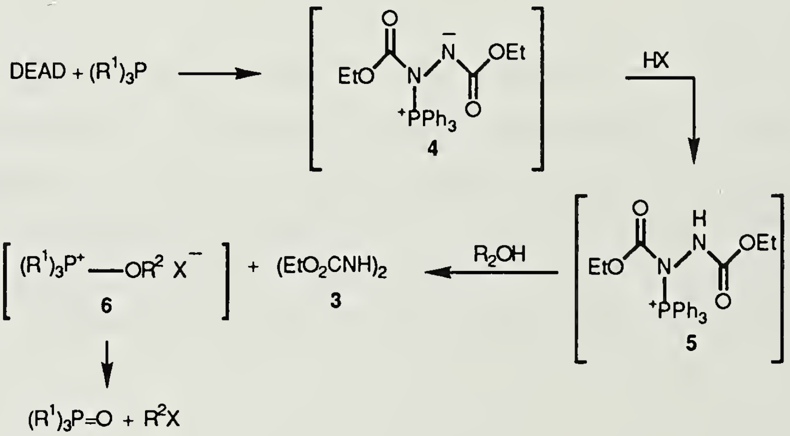
$$Ph_3P + RCO_2H + R^1OH \xrightarrow{\text{DEAD}} RCO_2R^1 + \underset{\mathbf{3}}{(EtO_2CNH)_2} \qquad (3)$$

(S)-(+)-2-octanol reacted with inversion of configuration to yield (R)-(-)-2-octyl benzoate.[4] Another important observation was that in the use of mixed primary-secondary diols, esterification occurred at the primary position indicating that primary alcohols can be selectively activated in the presence of secondary alcohols.[5] The significance of these results will be evident in the discussion below.

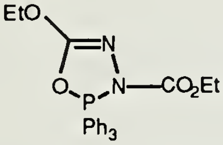
Huisgen reported in 1969 that the addition of Ph_3P to a dialkylazodicarboxylate resulted in the formation of a betaine **4**.[6] This report, and his own results, led Mitsunobu to propose that the mechanism began with formation of the betaine followed by protonation of the betaine **5** by the conjugate acid of the nucleophile, formation of an alkoxyphosphonium salt **6**, and S_N2 displacement (Scheme I).[1] Since this proposal, there have been several in-depth studies of the mechanism which show that the idea of activation is correct, but the reaction is not as simple as first suggested.

Scheme I



Betaine Stability

The formation of the betaine **4** is generally accepted as the initial step in the mechanism of the Mitsunobu reaction.[7] Since it is conceivable that Ph_3P can be oxidized to triphenylphosphine oxide with appropriate oxidizing agents without activating the hydroxyl group, it is important to know about the stability of the betaine. The betaine has been isolated and has a ^{31}P NMR shift of δ +44.9 ppm. The chemical shift remains relatively constant in various solvents: +43.9 ppm in benzene, +44.7 ppm in chloroform, and +45.4 ppm in DMF.[8] This implies that there is little if any equilibrium with Ph_3P and DEAD or with a cyclic phosphorane structure **7**. Further evidence for the irreversibility of the betaine formation was provided by Crich.[9] A 1:1 mixture of Ph_3P/DEAD gave the betaine (δ +43 ppm) and consumed all of the Ph_3P (δ -5.3 ppm). Addition of one equivalent of tributylphosphine (Bu_3P) afforded some triphenylphosphine oxide (δ +23 ppm) but no Ph_3P. The small amount of triphenylphosphine oxide was postulated to form as a result of hydrolysis of the betaine by some extraneous water. Addition of Ph_3P to the Bu_3P/DEAD betaine did not lead to the liberation of Bu_3P or the Ph_3P/DEAD betaine.



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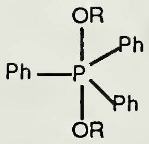
Oxyphosphonium Salt Formation

Mitsunobu proposed that alkoxyphosphonium salts **6** were formed in the pathway leading to the substitution products and triphenylphosphine oxide. There is now evidence for the formation of **6** as intermediates in the Mitsunobu reaction. Addition of a glucofuranose to Ph_3P/DEAD followed by fluoroboric acid gave rise to a single ^{31}P NMR peak at δ +65.2 ppm which is consistent with formation of an oxyphosphonium fluoroborate.[8] When Ph_3P was replaced by Bu_3P, the peak was shifted downfield to 103 ppm which would be expected due to less shielding by the substituents on phosphorus. Walker found that addition of trifluoroacetic acid to a Ph_3P/DEAD solution led to the protonated betaine, **5**. Addition of a secondary sterol to the protonated betaine solution slowly gave rise to a single ^{31}P NMR peak at δ +59 ppm.[10] Isolation by chromatography revealed this to be the oxyphosphonium salt, **6**. Addition of the acid to a solution of Ph_3P/DEAD and the alcohol yielded the same result.

Hughes also reported the presence of the oxyphosphonium salt of a ß-lactam alcohol as an intermediate.[7] He found that the rate of formation of the salt, **6**, decreased by 170 fold as the ratio of HCO_2H/HCO_2^- was increased by 4 fold. His studies indicated that the rate was first order in both the ß-lactam alcohol and the betaine, **4**. The rate was increased by 60 fold when the acid was changed from cyanoacetic acid [pKa(H_2O)=2.43] to formic acid [pKa(H_2O)=3.77] indicating that the rate is sensitive to carboxylate basicity.

Alkoxyphosphorane Formation

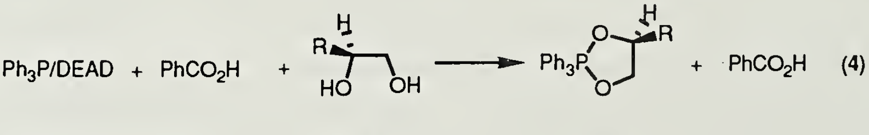
Some recent reports suggest that alkoxyphosphoranes may be the key intermediates leading to triphenylphosphine oxide and the substitution product instead of alkoxyphosphonium salts. In the esterification of carboxylic acids, Grochowski found that the addition of two equivalents of the alcohol to the betaine, led to the disappearance of the betaine and to the formation of an intermediate with a ^{31}P NMR shift of δ -63.0 ppm.[11] This peak was attributed to the presence of the dialkoxyphosphorane **8**. Addition of carboxylic acid to the intermediate led to the ester and triphenylphosphine oxide with no indication of formation of an alkoxyphosphonium salt. Jenkins



8

reported that the addition of a glucofuranose to the Ph3P betaine led to a ^{31}P NMR peak at δ -55 ppm which is consistent with an acyclic phosphorane.[8] This went on to form the oxyphosphonium fluoroborate.

The use of two different alcohols in the absence of the acid gave rise to three high field peaks which further supports the idea that an O,O-dialkoxyphosphorane is formed.[12] Walker found that the order of addition gave rise to different intermediates and that the dialkoxyphorphorane is only an intermediate when acid is added last.[10] Hughes claims that in the absence of acid neither MeOH or 2-butanol gave rise to a phosphorane at ambient temperature, but 2-butanol did at -20°C.[7] This led to the conclusion that phosphoranes of varying stability are formed in the absence of acid. Evans has reported that a 1,2-diol, **9**, which is added last generated a 1,3,2λ^5-dioxaphospholane, **10**, as shown in equation 4, and that the decreasing stability of σ-dioxaphosphoranes in the presence of acid follows cyclic > primary > secondary.[13] More recently, Jenkins has reported that both the phosphorane and the alkoxyphosphonium salt exist as intermediates in equilibrium, and variations in the reaction conditions can shift the equilibrium in favor of one over the other.[14]

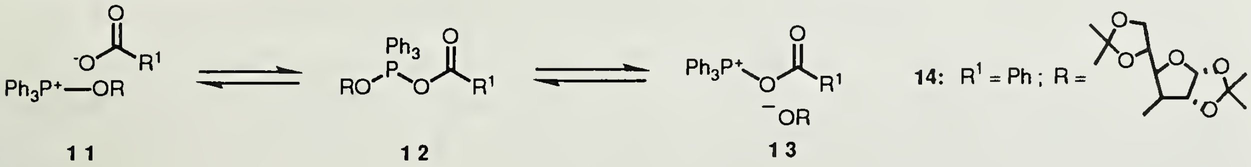


9 **10**

Acyloxy(alkoxy)phosphorane Formation

During the acylation of N-hydroxy compounds and phenols, Grochowski showed that an optically active phosphine led to a racemic phosphine oxide.[15] These data suggested that the reaction proceeded via an acyloxyphosphonium salt, followed by the formation of a pentacovalent (racemic) intermediate. However, there has been no other evidence suggesting that an acyloxy(alkoxy)phosphorane may be an intermediate in the Mitsunobu reaction until Jenkins recent report.[16] He found that the addition of benzoic acid to Ph3P/diisopropylazodicarboxylate (DIAD) and two equivalents of neopentyl alcohol gave rise to the dialkoxyphosphorane **8** and a compound with a ^{31}P chemical shift of -27.6 ppm. The peak was found to be solvent dependent with a limit of +62.6 ppm in acetonitrile. This was attributed to a fast equilibrium between the alkoxyphosphonium salt **11** and the corresponding acyloxy(alkoxy)phosphorane **12** (Scheme II). Successive additions of betaine to a mixture of the phosphorane and the alkoxyphosphonium salt shifted the alkoxyphosphonium salt peak upfield. Lowering the temperature to -100°C caused the peak to disappear in favor of two peaks attributed to **11** and **12**. Replacement of benzoic acid by p-nitrobenzoic acid or trifluoroacetic acid shifted the peak toward the ion pair as did increasing the polarity which is further evidence for the presence of **12**.

Scheme II



This may explain the observation that when **14** was heated the ester which formed had retained the configuration of the alcohol.[17] However, it is still believed that in most Mitsunobu esterification reactions, the acyloxy(alkoxy)phosphorane is only present as a "spectator" phosphorane.

Acid, Concentration, and Solvent Effects

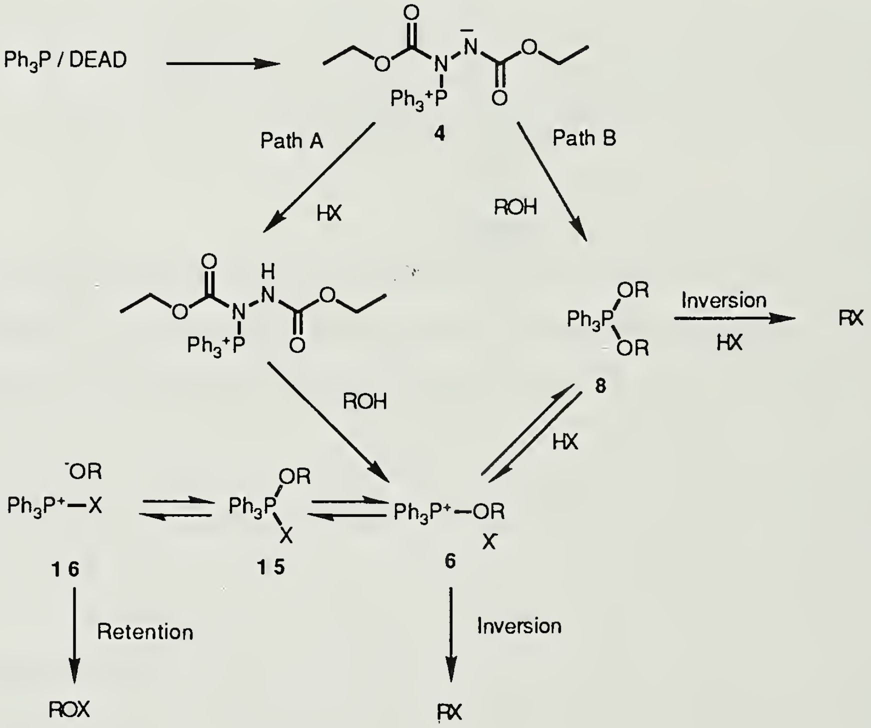
The recent reports by Hughes and Jenkins have provided a better understanding of the effect of reaction conditions upon the mechanism of the Mitsunobu reaction.[7, 14, 16] Hughes found that the addition of one equivalent of carboxylic acid led to a small amount of esterification of the alcohol, while two equivalents gave clean esterification. Presumably, the first equivalent of acid is used to protonate the betaine generating the carboxylate ion which nucleophilically attacks phosphorous leading to triphenylphosphine oxide. The second equivalent of acid decreases the reactivity of the carboxylate ion by H-bonding. Moreover, increasing acid solvation of the carboxylate ion reduces carboxylate thermodynamic basicity in the deprotonation of the alcohol and nucleophilicity toward saturated carbon in the S_N2 displacement step. The carboxylate basicity has little effect on the rate of S_N2 displacement. Since the alcohol activation step and the S_N2 displacement step vary greatly in their response to carboxylate basicity, this effect can be used to control which step is rate determining.

As previously mentioned, Jenkins found that the addition of benzoic acid to Ph_3P/DIAD and two equivalents of neopentyl alcohol gave rise to the dialkoxyphosphorane and the alkoxyphosphonium salt . Changing the order of addition gave the same results. In the presence of excess acid, only the oxyphosphonium salt was observed. It was noted that the ^{31}P NMR peak was sensitive to excess betaine which was attributed to establishing equilibrium with the (acyloxy)alkoxyphosphorane. The ^{31}P NMR shift for the alkoxyphosphonium salt was found to reach a limiting value with increasing amounts of acid, with acids of lower pKa, with increasing concentration, or with more polar solvents.

Current Understanding of the Mechanism

From the data presented, it is evident that the initial step in the mechanism of the Mitsunobu reaction is the irreversible formation of the betaine **4** as shown in Scheme III. If the acidic component is added first, path A is followed leading to the alkoxyphosphorane salt, **6**. The salt may be in equilibrium with **15** and **16** which can lead to the product with retention of configuration if HX is a carboxylic acid. However, the equilibrium apparently favors **6** which leads to the inverted product. If the alcohol is added first, it appears that path B is followed. The first intermediate formed is **8** which is in equilibrium with **6**. Depending on the reaction conditions, either **6** or **8** can lead to the inversion product.

Scheme III



RECENT SYNTHETIC APPLICATIONS

Since 1981, Mitsunobu's review has been cited over 400 times owing to its valuable use in synthetic organic chemistry. Quite obviously, it would be too difficult and space consuming to mention each of the synthetic uses of the reaction. However, a few of the more important applications which have appeared in the recent literature will be discussed.

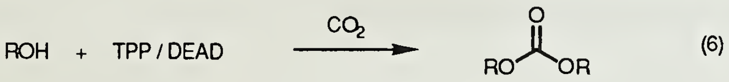
Preparation of Halides

In a recent attempt to synthesize antibiotics, an intermediate step involving preparation of a sensitive dienyl chloride from the corresponding alcohol proved difficult.[18] Proven methods for the conversion of alcohols to halides gave either poor yields or undesired products. However, the pure chloride was isolated when the alcohol was mixed with Ph_3P/DEAD in the presence of zinc chloride. Further studies showed that primary, secondary, and allylic alcohols were converted to the corresponding halides in 66-92% yield (equation 5). Moreover, the iodide, bromide, and chloride of the corresponding alcohol were obtained in comparable yield.

$$Ph_3P\ /\ DEAD\ +\ ROH \xrightarrow{ZnX_2} RX\ +\ Ph_3P{=}O \qquad (5)$$

Preparation of Carbonates

With the exception of mixing an alcohol with a chloroformate in the presence of base, most methods for the formation of carbonates result in low yields due to harsh conditions. Hoffman has reported that dialkyl carbonates **17** are prepared in 45-81% yield using the Mitsunobu reaction conditions (equation 6).[19]



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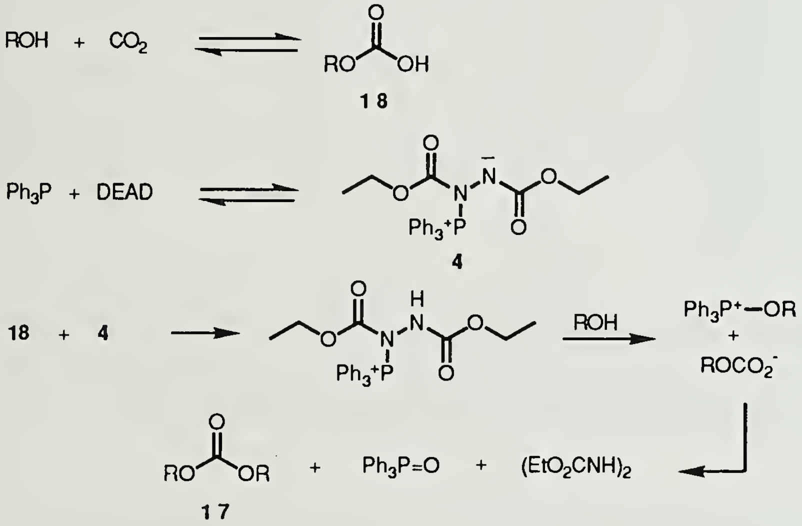
The reaction was shown to yield the desired carbonates from the addition of two equivalents of either a primary, secondary, or allylic alcohol. He postulated that the mechanism may be initiated by the formation of hemicarbonic acid (**18**) and the betaine **4** (Scheme IV).

Scheme IV

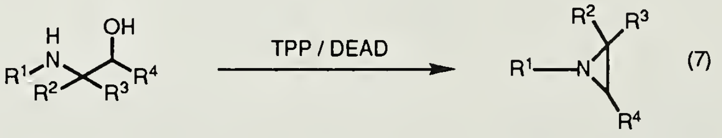


The betaine deprotonates the hemicarbonic acid which in turn deprotonates the second equivalent of alcohol. The alkoxide then attacks phosphorous to generate the alkoxyphosphonium salt which, upon S_N2 displacement generate the observed products as previously discussed. However, no evidence was provided supporting this mechanism.

Small Nitrogen-Containing Rings

Reports in the recent literature indicate that cyclization of amino and amido alcohols to the corresponding nitrogen-containing rings can be accomplished under the Mitsunobu reaction conditions.

The conversion of 2-amino alcohols **19** to aziridines **20** can usually be accomplished by employing either Ph_3P/carbontetrachloride/triethylamine or triphenylphosphine dibromide/triethylamine. However, treatment of unsubstituted 2-benzylaminoethanol and ephedrine with the dibromide reagent gave undesirable side products in both cases while treatment with Ph_3P/DEAD led to the corresponding aziridines (equation 7).[20,21] Table I lists some of the aziridines which have been prepared by this procedure.

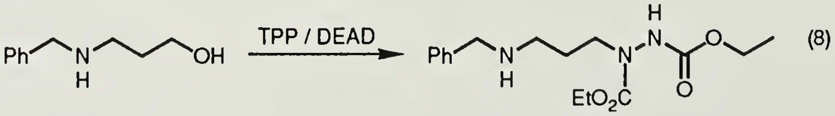


19 **20(a-e)**

Table I. Preparation of Aziridines from 2-amino alcohols under Mitsunobu reaction conditions

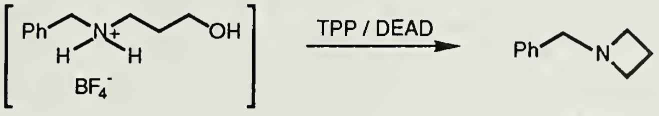
Product	R^1	R^2	R^3	R^4	Yield (%)
20a	Bzl	H	H	H	18
20b	Bzl	H	H	CH_3	90
20c	Bzl	CH_3	CH_3	H	89
20d	cHex	H	H	Ph	86
20e	CH_3	CH_3	H	Ph	84

Likewise, 3-aminoalcohols have been converted to the corresponding four-membered nitrogen-containing rings, azetidines.[22] When 3-(N-benzyl)aminopropan-1-ol (**21**) was mixed with Ph_3P/DEAD, a hydrazine derivative **22** was obtained (equation 8).[23]



21 **22**

In order to avoid this unwanted reaction, the nucleophilicity of the hydrazide anion was decreased by converting the amino alcohol to a salt. Both the tetrafluoroborate salt and the hydrobromide salt of the amino alcohol led to the desired azetidine **23** in 40-50% yield (equation 9).



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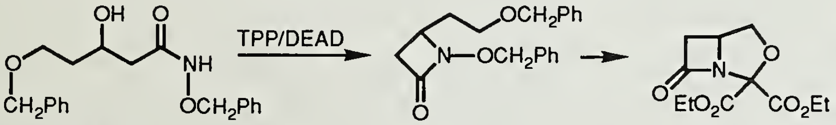
2 3

The β-lactam, which is of great clinical importance, is structurally similar to the azetidines. It is conceivable then, that β-lactams can also be formed in a cyclization step using Mitsunobu reaction conditions. Miller proved this by preparing a variety of β-lactams from β-hydroxy hydroxamic acids **24**.[23] He has since utilized this methodology in preparing an N-substituted β-lactam **25** as an intermediate in the synthesis of a bicyclo β-lactam **26** as shown in equation 10.[24]

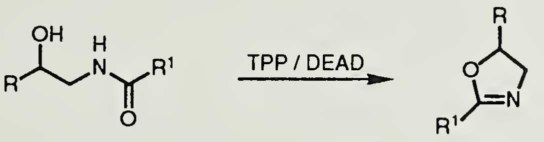
2 3



(10)

2 4 **2 5** **2 6**

When the hydroxyl group is situated on an N-alkyl substituted amide **27** and subjected to Mitsunobu reaction conditions, 2-oxazolines **28** will be formed (equation 11). Standard procedures for the preparation of 2-oxazolines require strongly acidic, basic, or thermal conditions. Roush found that these methods were not suitable for the preparation of 5-phenyl-2-oxazolines, but the much milder Mitsunobu conditions worked well for a variety of hydroxy amides.[25]



(11)

2 7 **2 8**

SUMMARY

The Mitsunobu reaction has been useful in the activation of alcohols for the preparation of several classes of compounds. While standard methods often employ harsh conditions, the Mitsunobu reaction is neutral and mild. Several in-depth studies have shown that variations in the

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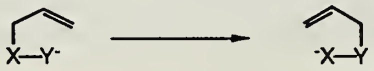
RECENT DEVELOPMENTS IN THE [2,3]-WITTIG REARRANGEMENT

Reported by Jack Amburgey September 18, 1989

INTRODUCTION

Sigmatropic rearrangements have been a mainstay in organic synthesis for several decades. The [2,3]-and [3,3]-sigmatropic rearrangements are powerful tools in the arsenal of synthetic organic chemists and have been the subject of intensive mechanistic investigations.[1] The former rearrangement is defined as a thermal isomerization involving six electrons in a five membered cyclic transition state (Scheme I).

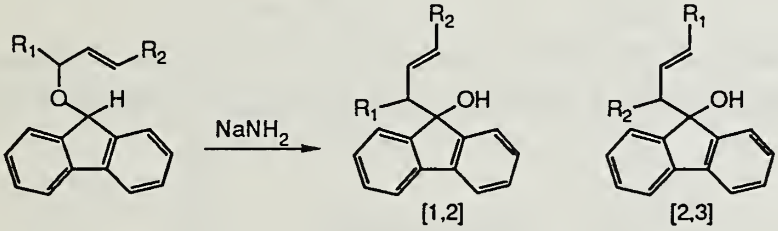
Scheme I



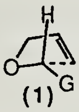
The scope of this rearrangement is largely due to the vast number of X and Y combinations possible. One such combination, where X = O and Y = carbanion, is the [2,3]-Wittig rearrangement.[2] In this review, recent developments in the [2,3]-Wittig rearrangement are discussed which post-date a review that has been published in 1986 by Nakai.[3]

The initial evidence for this rearrangement arose during the study of the [1,2]-Wittig rearrangement of allyl fluorenyl ethers (Scheme II).[4] As opposed to the stepwise, radical mechanism of the [1,2]-Wittig rearrangement, the [2,3]-Wittig rearrangement proceeds by a concerted suprafacial reaction which can be viewed as involving the highest occupied molecular orbital (HOMO) of the carbanion site and the lowest unoccupied molecular orbital (LUMO) of the allylic site.[5]

Scheme II



The transition state proposed for the rearrangement is a folded envelope (**1**).[3] This transition state explains important features of the [2,3]-Wittig rearrangement which include



(1)

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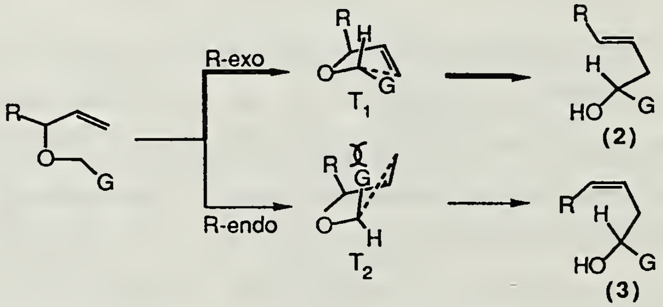
generation of specific olefin geometries, regiospecific carbon-carbon bond formation, and stereoselective creation of vicinal stereogenic centers.

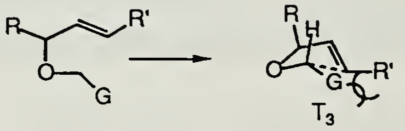
E-Z SELECTIVITY

The [2,3]-Wittig rearrangement of allylic ethers bearing alkyl substituents at the allylic position can rearrange to either (*E*) or (*Z*) olefins. Examination of the transition states (Scheme III) reveals that the preferred transition state (T_1) has the R substituent occupying the *exo* position thus leading to the (*E*) olefin (2).[6] When an additional R substituent is placed at the vinyl terminus of the allylic moiety (Scheme IV), the (*E*) selectivity decreases. This is due to an increased gauche interaction between G and the vinyl substituent on the allylic moiety as shown in T_3. This provides smaller differences in energy between transition states and thus poorer (*E*) selectivity.

Scheme III

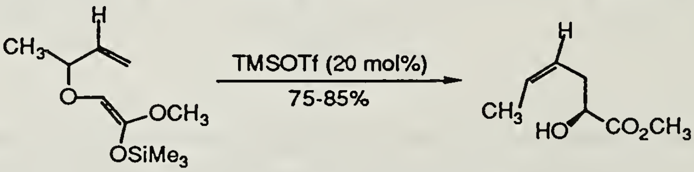


Scheme IV



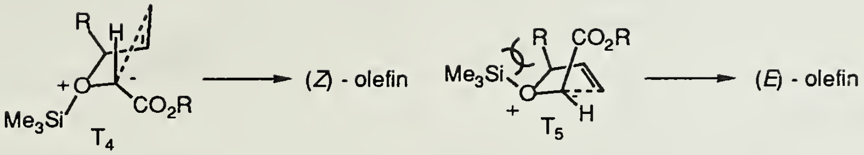
Recently, Nakai and co-workers reported the [2,3]-Wittig rearrangement of silyl ketene acetals of allyl oxyacetates which provided the rarely observed (*Z*) olefin selectivity (Scheme V).[7]

Scheme V



The reverse in selectivity was accounted for by the presence of an oxygen ylide[8] which can assume several transition states, two of which are shown in Scheme VI.

Scheme VI



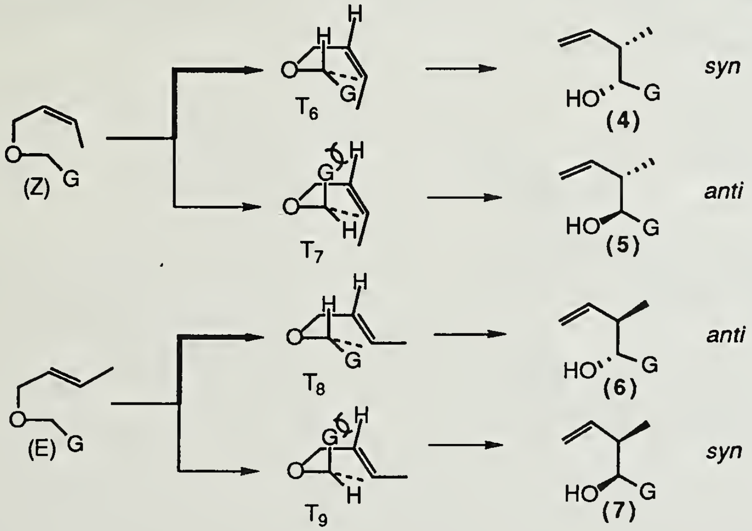
It can be seen that the second transition state T_5 contains large eclipsing interactions between the alkyl group and the $SiMe_3$ moiety whereas T_4 avoids this interaction as the R group assumes the *endo* position. This unique selectivity in conjunction with the mild conditions makes this rearrangement particularly useful for base-sensitive substrates.

DIASTEREOSELECTIVITY

Background

As previously described, the [2,3]-Wittig rearrangement has exceptional diastereoselection in the creation of two new vicinal stereogenic centers. An intensive study with a wide variety of [2,3]-Wittig variants revealed that (Z) olefins generally afford *syn* products where as (*E*) olefins give *anti* products.[3,9] This selectivity can be explained by the transition states shown in Scheme VII.

Scheme VII

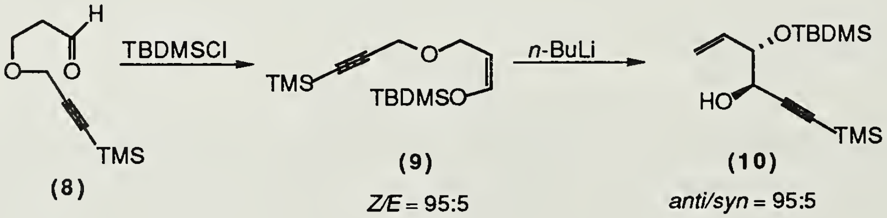


The transition states through which (*Z*) olefins give *anti* products (5) and (*E*) olefins give *syn* products (7) (T_7 and T_9) contain a pseudo-1,3-diaxial interaction between G and H. Thus, the preferred transition states for (Z) and (*E*) olefins are T_6 and T_8 respectively. A notable exception to this generality is the fact that when G = CO_2^- the opposite diastereoselectivity is observed. This can be explained by considering the increase in bulk of the carboxylate with respect to other typical groups used as G (vinyl and alkynyl). As G increases in bulk (in this case CO_2^-), the gauche interaction increases which prevails over the pseudo-1,3-diaxial interaction. Thus, the rearrangement proceeds predominantly through the alternate transition states T_7 and T_9.

Reverse Selectivity

An example of anti selectivity with (Z) olefins (G ≠ carboxylate) has recently been reported.[10] This was accomplished by silylation of the enolate of aldehyde **(8)** with TBDMSCl yielding the thermodynamically more stable (Z) olefin **(9)** followed by treatment with *n*-butyllithium (Scheme VIII). The isolated rearranged product was the 1,2-diol system **(10)** which exhibited high *anti* diastereoselection. This opposite trend in stereoselectivity can be explained by the large gauche interaction between the bulky TBDMS group and the pseudo equatorial alkyne in T_{10}. This interaction is eliminated by placement of the alkyne in the pseudo axial position which leads to the *anti* product through T_{11} (Scheme IX).

Scheme VIII

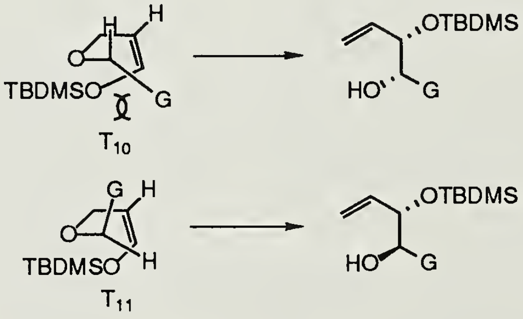


(8)

(9)
Z/E = 95:5

(10)
anti/syn = 95:5

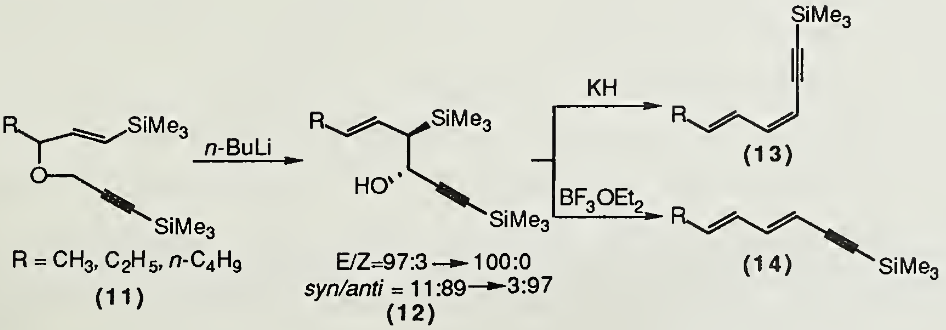
Scheme IX



In addition to the synthesis of polyhydroxylated natural products, this 1,2-diol system is of interest due to the numerous functional transformations that are available through alcohols.

The high stereoselectivity of the [2,3]-Wittig rearrangement was used in conjunction with a Peterson olefination[11] to afford high stereocontrol in the synthesis of conjugated trienes (Scheme X).[12] When the ether **(11)** was treated with *n*-BuLi, the [2,3]-rearrangement product **(12)** was obtained with good regio-and diastereoselectivity. Treatment of the β-siloxy alcohol with KH (*syn* elimination) or $BF_3 \cdot OEt_2$ (*anti* elimination) afforded the (3*Z*, 5*E*), **(13)** and (3*E*, 5*E*), **(14)** dienynes respectively.

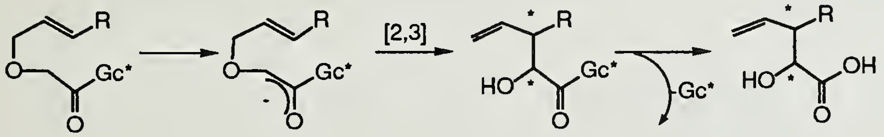
Scheme X



ASYMMETRIC SYNTHESIS

A general trend in organic chemistry in the past few years has been the development of reagents capable of controlling the absolute configuration of the products. This includes work in asymmetric aldol condensations,[13,14] alkylations,[15] cycloadditions,[13,16] reductions,[17] and hydrogenations.[13,18] These reactions employ chiral catalysts or chiral auxiliaries to form new stereogenic centers with high enantiomeric excess. This strategy can be applied to the [2,3]-Wittig rearrangement by incorporating a chiral auxiliary in the allyl ether to provide a substrate with a chiral enolate terminus (Scheme XI).

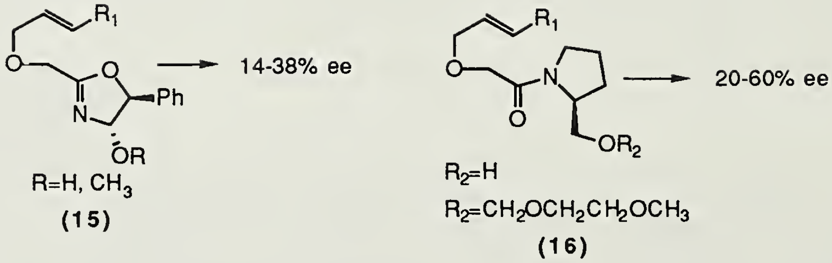
Scheme XI



The chiral auxiliary could be removed subsequently to produce a rearranged product containing one (R = H) or two (R = alkyl) newly created stereogenic centers.

Initial investigations of the use of chiral enolates employed in the [2,3]-Wittig rearrangement were performed by Nakai and co-workers.[19,20] They investigated the asymmetric [2,3]-Wittig rearrangement utilizing the chiral oxazolines **(15)** and amides **(16)** shown in Scheme XII. Results of this investigation were disappointing due to the low levels of enantio-and/or diastereofacial selectivity observed.

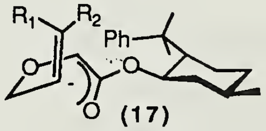
Scheme XII



(15)

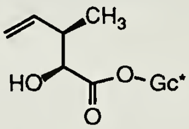
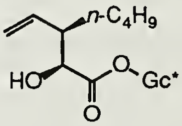
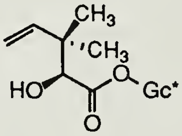
(16)

Recent studies involving the rearrangement of (*E*-2-alkenyloxy) acetates derived from (-)-8-phenylmenthol **(17)** have been shown to proceed with an extremely high level of diastereofacial selectivity along with high *syn* selectivity as shown in Table I.[21]

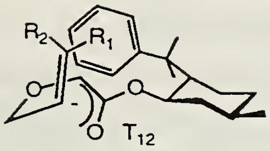


(17)

Table I. Rearrangements of (E-2-alkenyloxy) acetates derived from (-)-8-phenylmenthol.

substrate	base	product	*syn*/*anti*	d.e;%	config.
R_1=CH_3 R_2=H	LDA		90:10	97	2S
"	LHMDS	"	93:7	96	2S
"	LTMP	"	92:8	97	2S
R_1=*n*-C_4H_9 R_2=H	LDA		92:8	95	2S
R_1=R_2=CH_3	LDA		-	96	2S

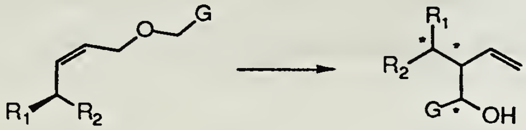
The 2(*S*) and *syn* preferences can be explained by the fact that enolization leads to the (E)-enolate which rearranges from the sterically less congested front side as shown in transition state T_{12}. In this transition state, the ester terminus is in the pseudo axial position in the envelope conformation[3] with the phenyl group situated at the back side.



The second possible transition state, in which the enolate undergoes rearrangement from the backside, suffers from steric repulsion between the phenyl group and the allylic substituent.

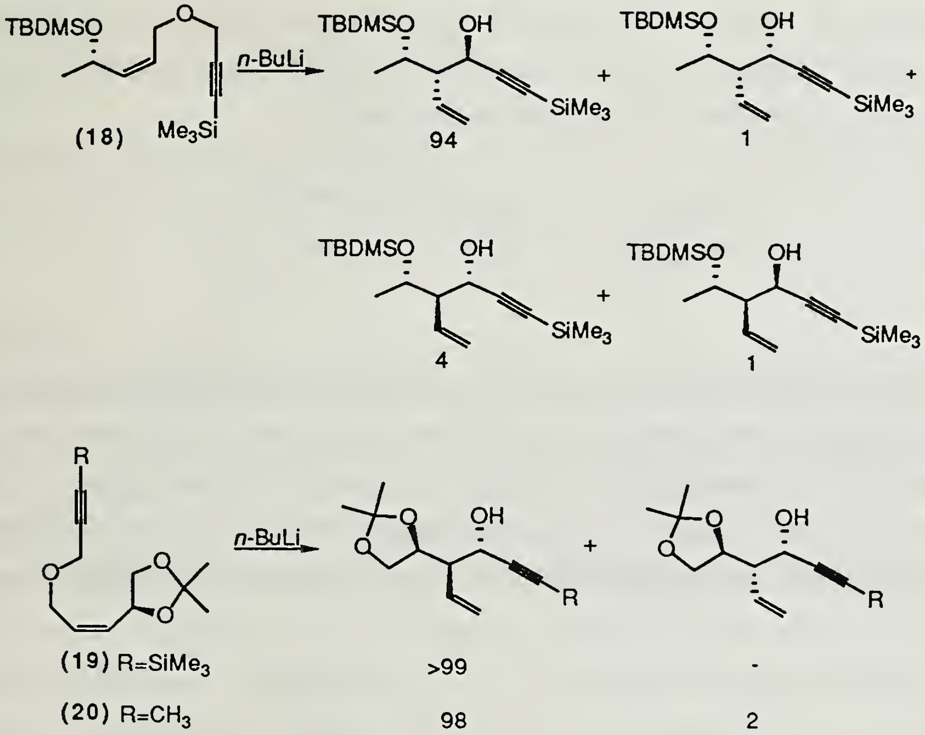
As can be seen, placing a chiral auxiliary in the G position has potential in asymmetric synthesis in controlling the absolute configuration in the [2,3]-Wittig rearrangement.[19,20,21] This type of asymmetric induction can also be achieved by placing a chiral substituent in the γ-position of the allylic ether (Scheme XIII). When successful, (high levels of internal and relative stereocontrol), stereocontrol could be maintained over three contiguous stereogenic centers.

Scheme XIII

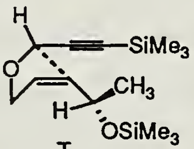


This methodology has been applied to allylic ethers derived from (*S*)-lactaldehyde and (*R*)-glyceraldehyde[22] as shown in Scheme XIV.

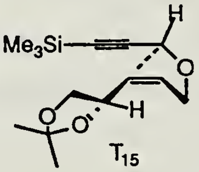
Scheme XIV



Examination of Scheme XIV reveals a high level of internal and relative stereocontrol in reactions of **18-20**. The high level of diastereoselectivity observed is typical of the acetylenic groups used (occupation of the pseudo equatorial position).[23,24] The most important feature of this rearrangement is the high level of relative stereocontrol observed. This high level of diastereofacial selectivity can be explained by the two transition states shown. In each case, the oxy-substituents are oriented perpendicular to the plane of the double bond thus minimizing allylic-1,3-strain. The attack of the carbanion may occur from two possible faces but will selectively attack from the face away from the oxy-substituent (to eliminate steric repulsion) thus leading to the high diastereofacial selectivity.



T$_{14}$

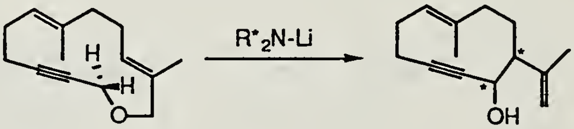


T$_{15}$

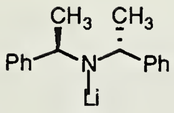
CHIRAL BASES

Although the use of chiral auxiliaries in the [2,3]-Wittig rearrangement has been shown to be very successful in terms of asymmetric induction, one can envision the utilization of chiral bases as a method of absolute stereocontrol. Work by Marshall and co-workers[25] has demonstrated the use of chiral bases as a method of achieving enantioselectivity in ring contractions in constructing intermediates in the total synthesis of aristolactone (Scheme XV).

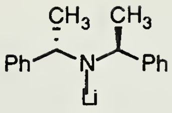
Scheme XV



It has been suggested that the purpose of the chiral base is to differentiate between the enantiotopic propargylic methylene protons. If selective proton abstraction is successful, the carbanion must retain its configuration during the reaction. The chiral bases chosen for the rearrangements were (*R*,*R*) and (*S*,*S*)-bis-(1-phenylethyl)amide ((**21**) and (**22**) respectively). Results of the [2,3]-Wittig rearrangement of the cyclic ether with several bases are shown in Table II.

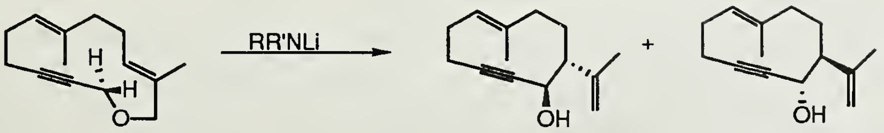


(R,R)
(21)

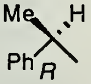
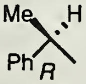


(S,S)
(22)

Table II. Enantioselective [2,3]-Wittig ring contractions.



(+)-2(R,R) (-)-2(S,S)

R	R'	T, °C	t, min	yield, %	$[\alpha_D]$	e.e., %
		-35 to -25	60	78	+33.4	73
R	*R*	-20	40	75	+28.5	57
S	*S*	-70 to -15	45	82	-32.9	64
S	*R*	-70 to 0	120	86	0	0

Rearrangements promoted by chiral bases **(21)** and **(22)** displayed moderate levels of enantioselectivity. Further studies will likely produce superior reagents than those used in this initial study.

CONCLUSION

In an effort to maximize the utility of the [2,3]-Wittig rearrangement in organic synthesis, researchers are continuing to develop new and interesting methods to accomplish this task. As shown, efforts to obtain (*Z*)-selectivity over the usual (*E*)-selectivity have been successful by the introduction of an oxygen ylide into the system. The unusual anti-selectivity with (*Z*) olefins has been accomplished by the introduction of a bulky TBDMS group in the vinyl position of the allyl ether. Finally, in conjunction with the growing progress in asymmetric synthesis, chiral auxiliaries, chiral substituents, and chiral bases have been used to introduce stereogenic centers in the [2,3]-Wittig rearrangement products. These new developments along with pre-existing methods can and will be used in the synthesis of many interesting and biologically active compounds in the future.

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TRANSITION METAL CARBENE COMPLEXES AND THEIR BENZANNULATION REACTION WITH ALKYNES

Reported by James E. Resek September 21, 1989

INTRODUCTION

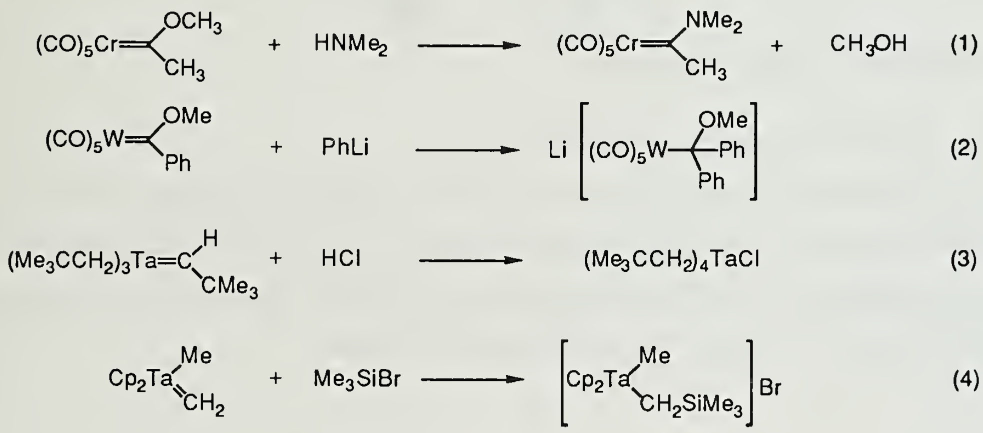
In 1964, Fischer and Maasbol completed the first synthesis of a transition metal carbene complex.[1] The 25 years since that discovery have seen great growth in the understanding of the chemistry of these interesting organometallic species. During this time, carbene complexes have also been recognized as useful reagents in organic synthesis. Several reactions with organic substrates involving these reagents have been intensively studied including olefin cyclopropanation,[2] olefin metathesis,[3] and [2+2]-cycloadditions to form β-lactams.[4] To date, however, the most synthetically useful reaction of chromium carbenes has been the benzannulation effected by reaction of the organometallic with an alkyne. This abstract will discuss carbene complexes as well as mechanistic and synthetic aspects of this reaction.

CARBENE COMPLEXES

Structure and Bonding of Metal Carbene Complexes

Transition metal carbene complexes are organometallic compounds that contain a metal-carbon double bond. They can be divided into two classes based on their chemistry. In "Fischer" type carbenes, the carbene carbon acts as an electrophile, and hence is attacked by bases or nucleophiles, as illustrated in equations 1 and 2 of Scheme I. In both cases the carbene carbon is attacked by the base. In the first case the presence of a leaving group results in a substitution reaction that forms a new carbene, while in the second case a discrete complex is formed.

Scheme I



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In "Schrock" type carbenes the carbene carbon acts as a nucleophile and thus is attacked by electrophiles, as shown in reactions 3 and 4 of Scheme I.

Figure 1 depicts the three limiting resonance forms used to describe carbene complexes in valence-bond terms.[6] Nucleophilic carbenes are best described by form I. These compounds have a "true" metal-carbon double bond. In electrophilic carbenes, a significant amount of the stabilization of the electron deficient carbene carbon is contributed by the X and Y groups. Consequently, though all carbene complexes are generally written in form I, electrophilic carbenes have significant contribution from forms II and III. This is supported by bond length data from X-ray crystal structure analysis. The crystal structure of $(CO)_5CrC(OEt)(NMe_2)$ shows a C-N bond length of 1.33Å, which is shorter than the normal 1.45Å observed for single bonds between sp^2 carbon and nitrogen. The C-O length is similarly decreased from the normal value of 1.41Å to 1.35Å. This indicates that there is significant multiple bond character between the carbene carbon and its substituents.[8a] The reactions described herein are characteristic of electrophilic carbenes.

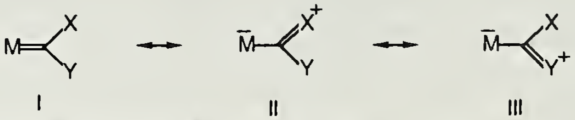


Figure 1. Resonance Structures of Carbene Complexes.

Electrophilic carbene ligands generally have a heteroatomic substituent. They can be recognized as species that have singlet ground states as free carbenes. Bonding in these complexes can be viewed as shown in Figure 2.[7] The singlet carbene ligand can be considered to be a neutral two-electron donor, and the metal can back bond by donation from a filled metal d orbital into the vacant carbon p orbital.

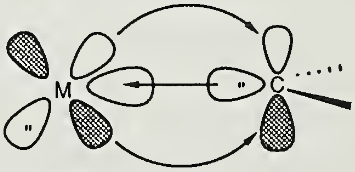


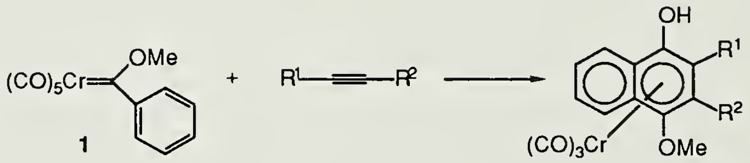
Figure 2. Bonding in Carbene Complexes.

Preparation of Metal Carbene Complexes

The most commonly employed method for the synthesis of chromium carbene complexes was developed by Fischer.[9] In a typical example depicted in Scheme II, chromium hexacarbonyl is treated with phenyllithium, and the resulting acylate complex is alkylated with trimethyloxonium tetrafluoroborate to give the desired chromium carbene complex.

interesting mechanistic puzzle, and a potentially valuable method for the rapid construction of complex ring systems.

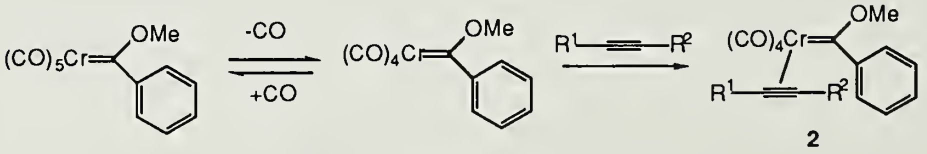
Scheme IV



Mechanistic Considerations

Kinetics. Dötz has reported some kinetic studies of the benzannulation reaction.[13] The presence of a carbon monoxide atmosphere decreased the reaction rate. This suggested that the first step of the benzannulation was the loss of CO from the carbene complex to form a coordinatively unsaturated species. Both the alkyne and CO can coordinate to the activated organometallic moiety. Kinetic measurements show that the readdition of CO is faster than the coordination of the alkyne. These data suggest that the substitution of alkyne for CO occurs by a dissociative mechanism (Scheme V). The activation enthalpy and entropy has been determined for the reaction of carbene complex **1** and diphenylacetylene, and the data obtained ($\Delta H^{\ddagger}=108\pm2$ kJ/mol, $\Delta S^{\ddagger}=26\pm6$ J/mol•K) are similar to those obtained in another reaction of chromium carbenes that occurs by a dissociative mechanism.[13b] Subsequent steps are more difficult to study because they occur after the rate determining step.

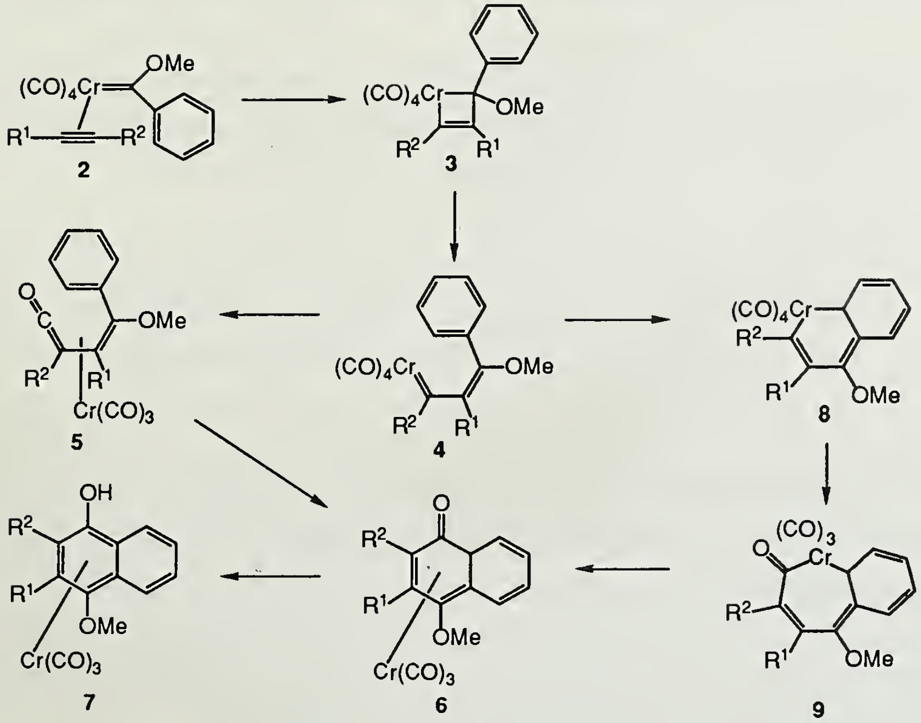
Scheme V



Mechanistic Proposals. Dötz and Casey have both proposed mechanisms for phenol formation in the reaction of alkynes with chromium carbene complexes. These are depicted in Scheme VI. Each proposal begins with the cyclization of the alkyne complex **2** to the chromacyclobutene **3**. This is thought to then undergo an electrocyclic ring opening to form the vinyl carbene complex **4**. From here, Dötz proposed a rearrangement to the vinylketene complex **5**, which then undergoes ring closure and tautomerization to provide the benzannulated product **7**.[5]

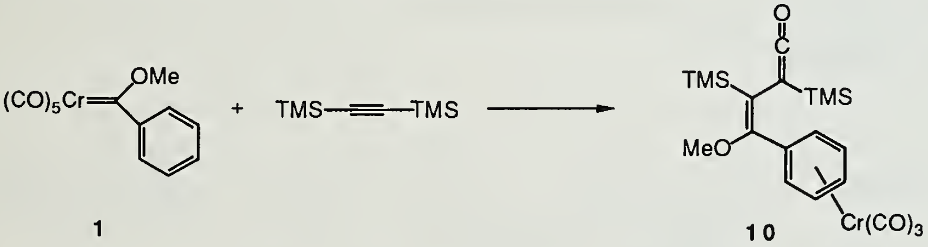
Casey suggested an electrocyclic ring closure of the vinyl carbene complex **4** to give the six membered metallacycle **8**. Insertion of CO to form **9** is followed by rearrangement to **6** and tautomerization, to afford the observed product.[14]

Scheme VI



Vinylketene intermediates. A great deal of effort has been directed toward the detection of a vinylketene in the reaction mixture. This is the key intermediate proposed by Dötz, and its detection would provide strong support for this mechanism. The strongest evidence for the intermediacy of vinylketenes in the benzannulation reaction is the isolation of vinylketenes in the course of the reaction (Scheme VII). When the chromium carbene complex **1** is allowed to react with bis(trimethylsilyl)acetylene, the product isolated is vinylketene **10**.[15]

Scheme VII

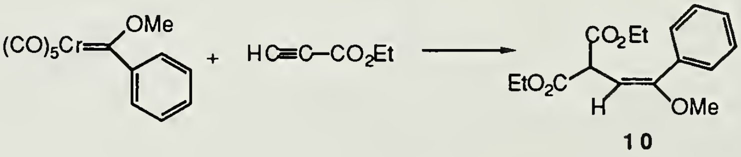


Originally, the isolation of the vinylketene was explained by steric interactions between the trimethylsilyl groups. According to this argument, the interaction prevented the vinylketene intermediate from adopting the s-cis conformation necessary for the succeeding ring closure. It was later found that a reaction with trimethylsilylacetylene also gave some vinylketene product,[16] while the more sterically demanding *tert*-butylacetylene gave exclusively benzannulated product.[17]

This indicates that in addition to steric effects, the stabilizing ability of silyl groups on vinylketenes is involved.

The presence of vinylketenes in the reaction mixture has also been demonstrated by trapping experiments. One example reported by Yamashita showed that performing this reaction in the presence of ethanol yields the expected vinylketene trapped as an ester.[18]

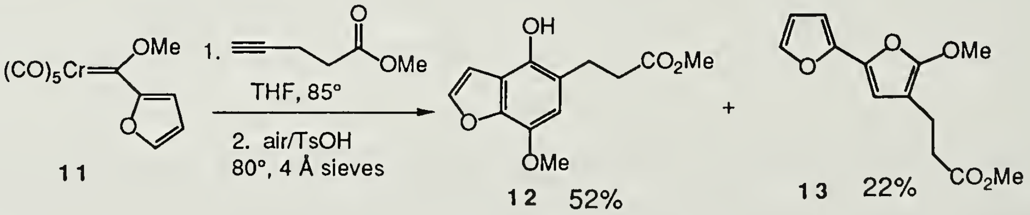
Scheme VIII



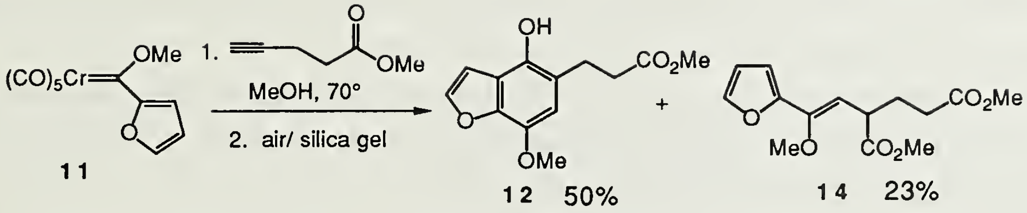
It must be noted here that while both the isolation and trapping experiments support the Dötz mechanism, they provide only circumstantial evidence. The fact that vinylketenes were isolated from the benzannulation mixture does not necessarily imply that these species lie on the pathway to the 4-alkoxyphenol. It is equally possible that vinylketenes could be the product of a side reaction favored when stabilizing silyl groups are present. Similarly, trapped vinylketenes may only be the result of a non-productive side path of the mechanism.

Stereochemical Features of the Mechanism. Wulff has recently added some interesting insight to this mechanistic problem. As part of the total synthesis of the angular furanocoumerin, sphondin, the reaction of the (2-furyl)carbene complex **11** with methyl 4-pentynoate was studied. The reaction, depicted in Scheme IX, gave a 52% yield of the desired benzannulated product **12**, as well as a 22% yield of the (5-furyl)furan **13**.[19] Furan products had been previously reported for benzannulation reactions,[24] though they usually represented a minor product. In this case only the benzannulated product and the furan product were observed, and Wulff speculated that study of this reaction could provide valuable information on the mechanisms of formation of both products.[20]

Scheme IX

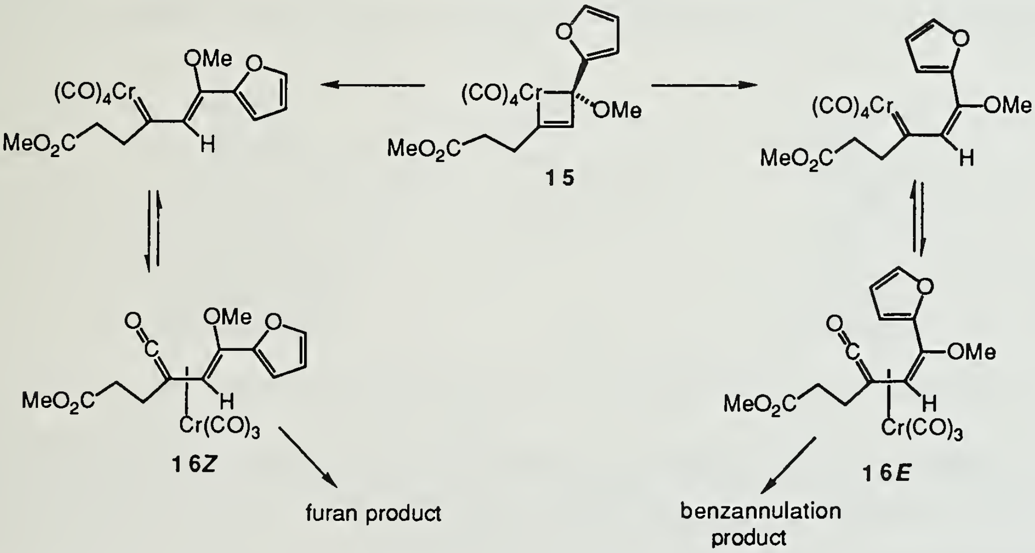


Scheme X



Towards this end, the same reaction was run in the presence of methanol in an attempt to observe vinylketenes in the reaction mixture. The results are reported in Scheme X. Interestingly, the benzannulated product **12** was obtained in 50% yield, but none of the furan product **13**. Instead, the enol ether **14** was isolated in 23% yield. A single diasteriomer of **14** was obtained, and this was determined to be the *Z* isomer. The fact that the ratios of the products remained essentially equal, and the furan product was replaced exclusively by the *Z* isomer of **14** suggested that stereochemistry needed to be considered in the proposed mechanisms. In the context of the Dötz mechanism, Wulff suggested that the chromacyclobutene intermediate **15** undergoes a *nonreversible* electrocyclic ring opening to produce both *E* and *Z* isomers of the vinylketene complex **16**. As shown in Scheme XI, only the the vinylketene complex **16*E*** can assume the necessary conformation for ring closure leading to the benzannulated product. Any intermediate **16*Z*** formed apparently leads to the furan product.[20]

Scheme XI



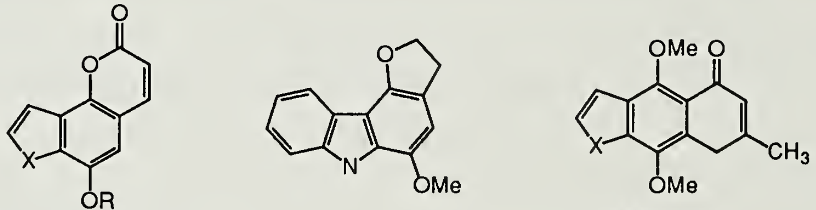
The results in Scheme XI are presented in terms of the Dötz vinylketene mechanism. These results do not by any means eliminate the Casey mechanism. In this mechanism, the chromabutadiene must have the *E* configuration to close to the six membered metallacycle that is suggested as the key intermediate.

The mechanism of the benzannulation of alkynes with chromium carbenes is still far from understood. However, this is the first piece of evidence that links the stereochemistry of an intermediate with the identity of the products observed.

Applications in Organic Synthesis

The benzannulation reaction has been applied to the synthesis of many compounds, such as **22**,[19] **23**,[21] and **24**.[22] One advantage to the use of the benzannulation is the relative ease with which natural product analogs can be prepared. This is true because chromium carbene complexes are readily converted to analogs by the methods previously discussed. This is illustrated in the synthetic products shown in Figure 3. The naturally occuring compound **22a** was synthesized using the benzannulation reaction as a key step. Use of a thiophene substituted carbene complex instead of a furyl carbene under similar reaction conditions allowed for the synthesis of the unnatural thiophene derivative **22b**. This same strategy was used in the preparation of structural analogs of khellin (**24a**). As is shown, syntheses of the pyrrole analog **24b**, and the phenyl analog **24c** were also achieved. Progress on other syntheses has been reported.[27]

The benzannulation reaction can be effected with oxygen and sulfur substituted carbene complexes, though the vast majority of examples reported employ alkoxy substituents.[8c,26]



22a: X = O
22b: X = S

23

24a: X = O
24b: X = N-CH_3
24c: X = HC=CH

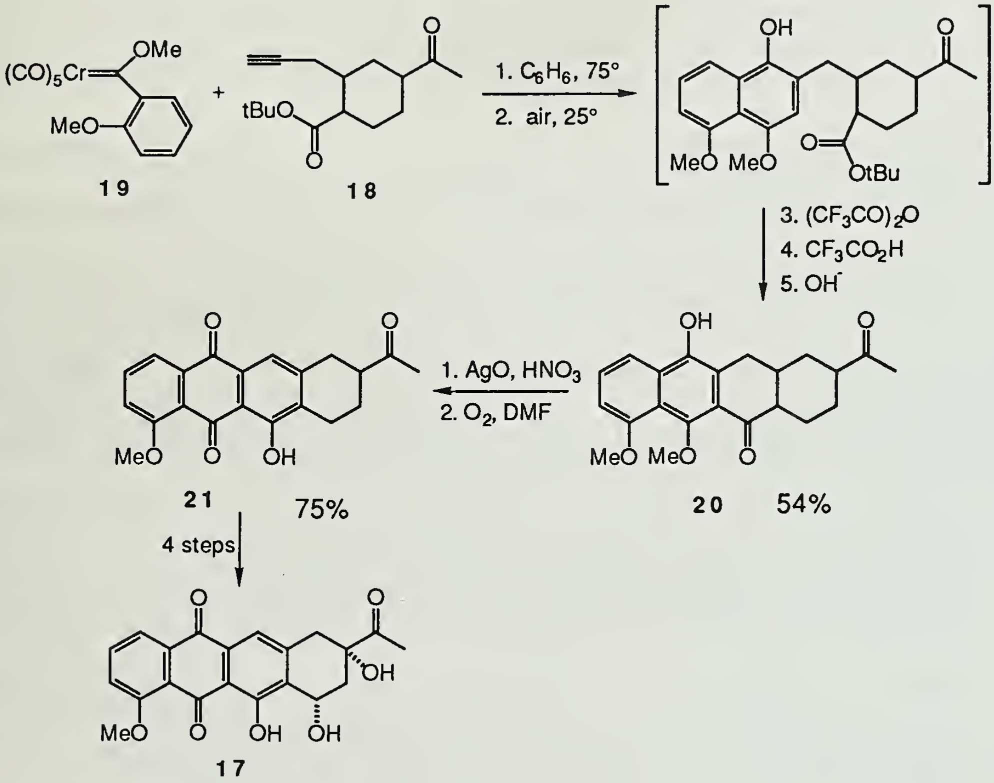
Figure 3. Products Synthesized Recently Using the Benzannulation Reaction.

Another attractive feature is the regioselectivity of the reaction. When the reaction involves a terminal alkyne, annulation takes place with high regioselectivity. The major product is always the 2-substituted phenol, and often it is the only product.[17,25]

The formal synthesis of the anthracycline, 11-deoxydaunomycinone (**17**), devised by Wulff is a representative example of the application of the benzannulation reaction. The synthesis, which includes a remarkable one-pot "double cyclization" sequence, is depicted in Scheme XII.

The alkyne **18** is allowed to react with the chromium carbene complex **19**. The adduct is then stirred in air to oxidatively remove the chromium, and release organic product. The hydroxyl group of the phenol is protected, and treatment with trifluoroacetic acid catalyzes cleavage of the *tert*-butyl ester and the Friedel-Crafts acylation that completes the construction of the tetracyclic system. Basic workup provides **20**. Treatment of **20** with silver(II) oxide induces aromatization of the C ring, and oxidation with molecular oxygen affords **21** in 42% yield from **18**. This completes a formal synthesis of 11-deoxydaunomycinone (**17**), which has been synthesized in 45% yield in four steps from **21**.[23]

Scheme XII



SUMMARY

The reaction of chromium carbene complexes with alkynes produces 4-alkoxyphenols in high yield and purity. The reaction mechanism is still far from understood, though there is a great deal of circumstantial evidence for the intermediacy of vinylketenes. Recent experiments have also suggested that a nonreversible electrocyclic ring opening is part of the mechanism. In spite of the incomplete understanding of the mechanism, the benzannulation reaction has been utilized in the syntheses of a variety of natural products, and promises to figure prominently in future synthetic and mechanistic research.

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THE MECHANISM OF OXYGEN TRANSFER FROM HETEROATOMS TO PHOSPHORUS

Reported by Mitchell L. Kurtzweil October 5, 1989

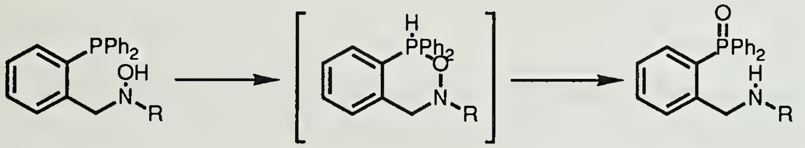
INTRODUCTION

A number of studies on the mechanism of oxygen transfer from various heteroatoms to phosphorus have been carried out. The transfer of oxygen from hydroxylamines,[1] N-oxides,[2] peroxides,[3] sulfenates,[4] and sulfoxides[5] to phosphines, phosphites, and other phosphorus-containing molecules has been examined with varying degrees of scrutiny and a number of mechanisms have been proposed for these reactions. This seminar will briefly review the mechanistic aspects of oxygen transfer from nitrogen, oxygen, and sulfur to phosphorus.

HYDROXYLAMINES

Preliminary work by Luckenbach on the reaction of hydroxylamine hydrochloride with an optically active phosphine showed that oxygen transfer proceeded with 73% retention of configuration at phosphorus to give the phosphine oxide.[1a] Stec and Okruszek carried out a more extensive set of experiments using an optically active phosphine and hydroxylamine and its hydrochloride salt. They proposed different mechanisms for the transfer of oxygen to phosphorus which depended on whether the hydroxylamine was in its free base form or its hydrochloride salt.[1b]

More recently, Beak and Loo have used the endocyclic restriction test to investigate the system shown in equation 1.[1c] They proposed an addition-elimination mechanism which involves the intermediate **2**. This was based mainly on overall first-order kinetics and a double labelling crossover experiment in which ^{18}O-labelled **1b** was reacted in the presence of **1a** to give only **3a** and ^{18}O-labelled **3b**.



(1)

1a, R = CH_3
b, R = i-Pr

2

3a, R = CH_3
b, R = i-Pr

N-OXIDES

The transfer of oxygen from an N-oxide to phosphorus is usually interpreted as attack by nucleophilic oxygen on phosphorus which acts as an electrophile. This is based in large part on

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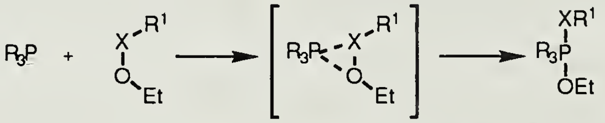
the findings by Ramirez that the rate of oxygen transfer from pyridine N-oxide to phosphorus occurs according the series $PCl_3 > PhPCl_2 > Ph_2PCl > Ph_3P$.[2a]

Stec observed >90% retention of configuration at phosphorus for the reaction of both aliphatic and aromatic N-oxides with an optically active phosphine to give the corresponding phosphine oxide and aliphatic or aromatic amines.[2b] Based on these results a mechanism was proposed in which the oxygen of the N-oxide attacked phosphorus to give a transition structure that was trigonal bipyramidal and placed the resulting P-O bond in an apical position.

PEROXIDES AND SULFENATES

Denney and co-workers have extensively studied the reaction of dialkylperoxides[3d] and alkyl benzenesulfenates[4] with phosphines, phosphites, and other tertiary phosphorus compounds. In both cases a biphilic insertion of phosphorus into the oxygen-heteroatom sigma bond was proposed as illustrated by transition structure **4** in equation 2. Support for this type of mechanism is based on an inversion of reactivity for nucleophilic phosphorus compounds towards the oxygen-heteroatom linkage as compared to the reaction of ethyl iodide with phosphorus compounds and on a negligible solvent effect on reaction rates indicating a transition state with little or no ionic character.



(2)

4, XR^1 = OEt, SPh

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CHIRAL AUXILIARIES AND CATALYSTS FOR ASYMMETRIC DIELS-ALDER REACTIONS -RECENT ADVANCES-

Reported by Dongchul Lim October 9, 1989

INTRODUCTION

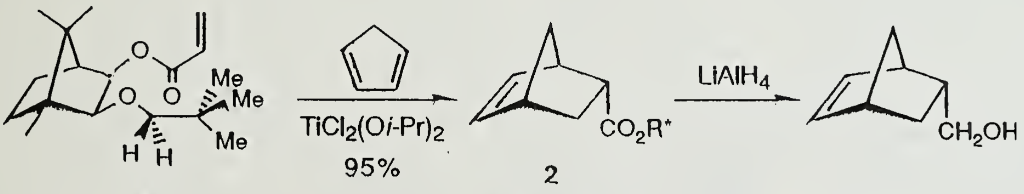
The Diels-Alder reaction holds great promise in asymmetric synthesis because up to four new stereocenters are formed at the bonding loci with predictable relative configurations. For the past two decades, there has been an enormous effort to achieve high level of absolute stereocontrol in the Diels-Alder reaction.[1] The simplest method is the temporary attachment of a chiral auxiliary to the dienophile or diene. After the cycloaddition has been performed, the auxiliary is removed and recycled. Using the chiral auxiliaries derived from menthol, lactate, camphor sulfonamides, and amino alcohols, almost complete enantioselectivity has been achieved. Another method for π-facial differentiation in Diels-Alder reactions is the employment of a chiral Lewis acid. This review will discuss the recent developments in chiral auxiliaries and catalysts for asymmetric Diels-Alder reactions.

CHIRAL DIENOPHILES

Acrylates

Menthol and Camphor-Derived Acrylates.[2-5] First auxiliary group for asymmetric Diels-Alder reaction was reported by Walborsky in 1963.[2] The reaction of bis(menthyl)fumarate derived from menthol with 1,3-butadiene catalyzed by $TiCl_4$ afforded the cyclohexene derivative with 80% yield and 78% de. In 1975, Corey et al.[3] reported that the addition of 8-phenylmenthyl acrylate to cyclopentadiene in the presence of $TiCl_4$ proceed with 90% de. The high stereocontrol observed with the 8-phenylmenthol stimulated a search for more practical auxiliary alcohols. Towards that end, *cis*-3-hydroxyisobornyl neopentyl ether **1** was found to be dramatically superior to 8-phenylmenthol in stereoselection and practicality (Scheme I).[4]

Scheme I



endo/exo = 24/1
endo de = 99.2%

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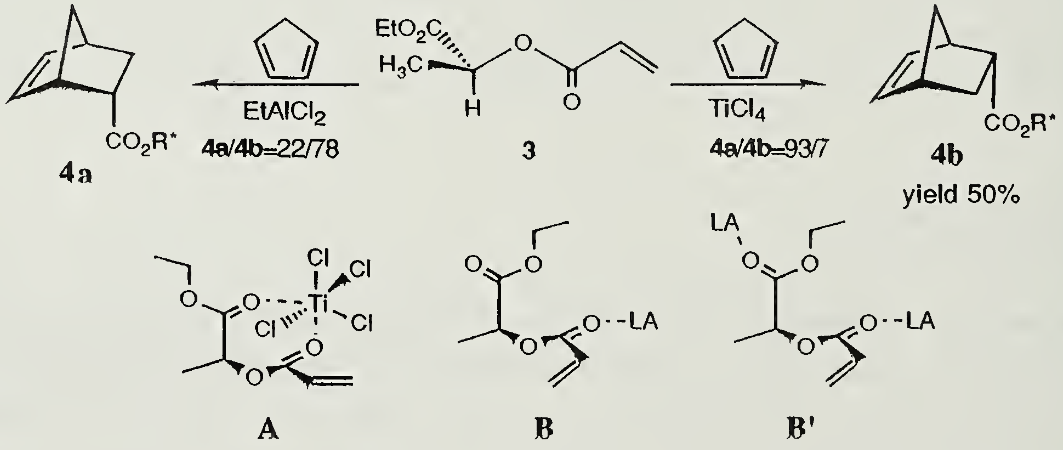
The reaction of acrylates derived from this ether with cyclopentadiene catalyzed by the mild Lewis acid $TiCl_2(Oi\text{-}Pr)_2$ afforded the cycloaddition adduct **2** in high chemical yield with high endo and diastereoselectivity.

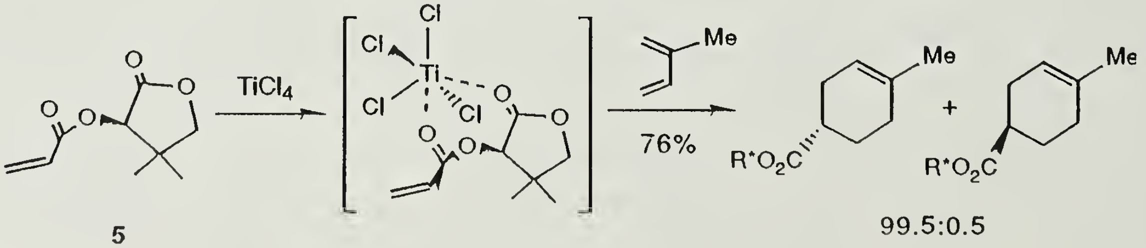
Lactate-Derived Acrylates.[6] Helmchen et al.[6a] studied the addition of the the acrylate of (*S*)-ethyl lactate **3** to cyclopentadiene. Interestingly, this reaction proceed with up to 93 % C_α-*si*-face selection in the presence of $TiCl_4$, whereas 78% C_α-*re*-face selection was observed using $EtAlCl_2$ (Scheme II). To rationalize this observation, the *s-syn* acrylate-$TiCl_4$ complex **A**, which was structurally defined by X-ray crystallography,[6b] was assumed to be in equilibrium with complexes **B** and **B'** (Scheme II). Decrease in stereoselectivity at higher $TiCl_4$ concentration and C_α-*re*-face selection with tetracoordinating Lewis acid $EtAlCl_2$ were explained by this proposal.

Scheme II



A valuable conclusion drawn from this proposal is that stabilization of complexes of type **A** should raise the diastereoselectivity. Thus, conformationally locked D-pantolactone **5** was examined as a chiral auxiliary.[6c] As expected, the addition of the acrylate of D-pantolactone to cyclopentadiene, isoprene, and butadiene in the presence of $TiCl_4$ proceeded with very high diastereofacial selectivity (Scheme III).

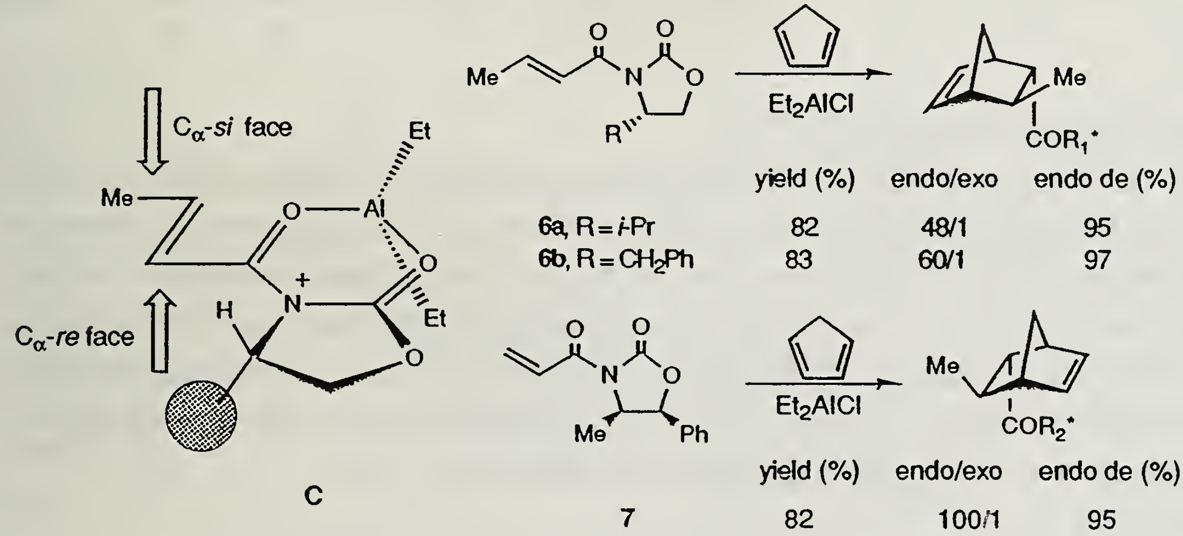
Scheme III



N-Acryloyl and N-Crotonyl compounds

α,ß-Unsaturated N-Acyloxazolidinones. Evans et al.[7] reported that Diels-Alder reactions of chiral α,ß-unsaturated N-acyloxazolidinones 6 and 7 with various dienes in the presence of Et_2AlCl proceeded very rapidly with excellent stereoselectivity (Scheme IV). To account for the rapid rates and endo/exo selectivities, a cationic Lewis-acid complexed dienophile C was proposed as shown in Scheme IV. Intramolecular cycloadditions of trienimides and cycloadditions of less reactive dienes such as isoprene and piperylene also proceeded with high diastereoselectivity. However it was reported that *Z*-unsaturated imide dienophiles undergo *Z* to *E* olefin isomerization and disubstituted unsaturated imide dienophiles show poor diastereofacial selectivity. Nevertheless the availability of chiral auxiliaries and high reactivity and stereoselectivity make unsaturated oxazolidinones attractive choices for many asymmetric Diels-Alder reactions.

Scheme IV

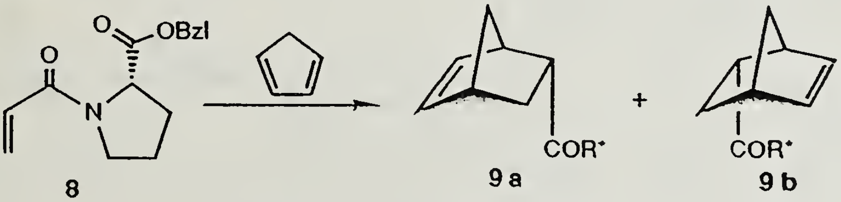


	yield (%)	endo/exo	endo de (%)
6a, R = *i*-Pr	82	48/1	95
6b, R = CH_2Ph	83	60/1	97

	yield (%)	endo/exo	endo de (%)
7	82	100/1	95

N-Acryloyl-(*S*)-Proline Benzyl Ester.[8] The $TiCl_4$-catalyzed Diels-Alder reactions of the proline acrylamide benzyl ester with cyclopentadiene showed very similar results to those obtained by using the acrylate of (*S*)-ethyl lactate 3 in Scheme II. Depending on the catalysts used, either the 5*R* product **9a** or the 5*S* Product **9b** was formed in excess (Scheme V).

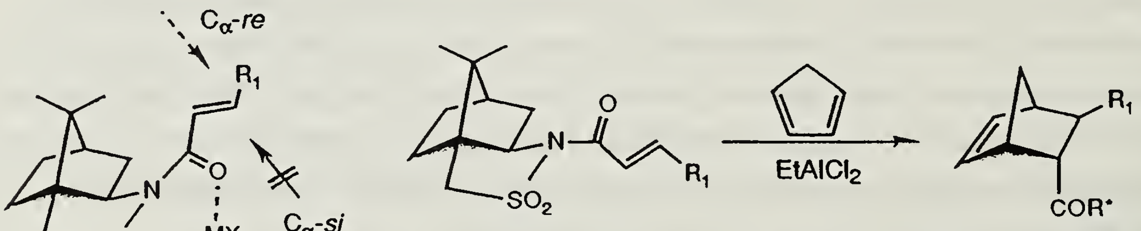
Scheme V



Catalyst	Yield (%)	Endo/exo	9a/9b
$TiCl_4$	53	94:6	97:3
$EtAlCl_2$	96	92:8	10:90

N-Acylsultams Derived from Camphor.[9] Camphor-derived *N*-acyl sultams **10** have shown exceptional reactivity and stereoselectivity in Diels-Alder cycloadditions in the presence of $EtAlCl_2$ or $TiCl_4$ at very low temperature. To rationalize these observations, the SO_2 and C=O groups were proposed to be chelated by the metal which directs the diene to the less hindered C_α-*re*-face of the conformation **D** (Scheme VI).

Scheme VI



D

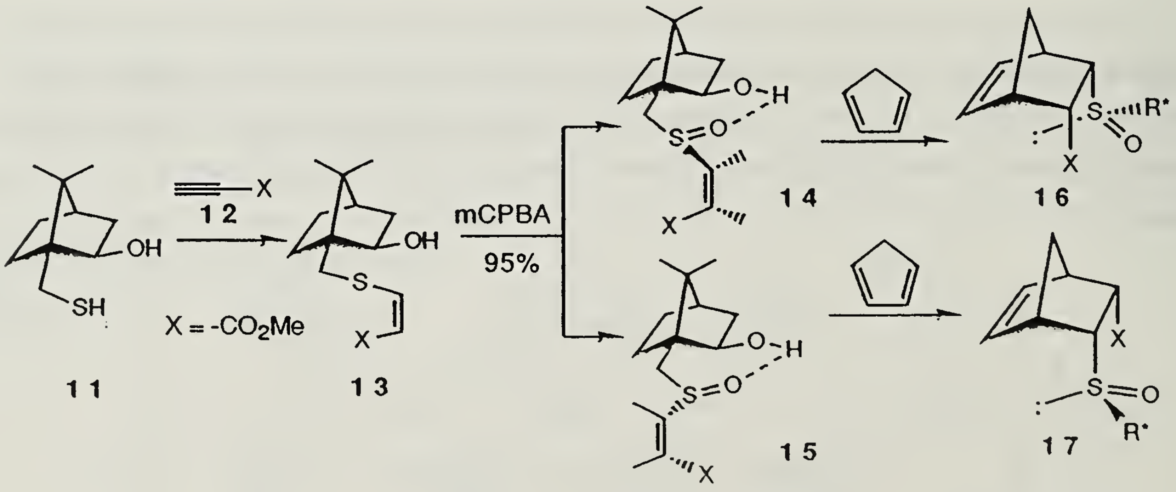
10

R1	Yield (%)	Endo (%)	d.e. (%)
H	93	99.5	93
CH_3	91	96	98

Chiral Sulfinyl Dienophiles[10]

Chiral vinyl sulfoxides have been utilized in asymmetric Diels-Alder reactions with good endo and diastereoselectivity. Michael addition of hydroxythiol **11** to acetylene **12** afforded the corresponding adduct **13** with *Z*-selectivity. The hydroxyl group-directed oxidation of the vinyl sulfide **8** with mCPBA gave the vinyl sulfoxides **14** and **15** with high diastereoselectivity in favor of **14**. When the 96:4 mixture of sulfoxides **14** and **15** were combined with cyclopentadiene, two diastereoisomers **16** and **17** were detected in the ratio of 98:traces. This indicates that the cycloaddition of the sulfoxides is highly diastereoselective (Scheme VII).

Scheme VII



14/15 = 96/4

yield 90%

16/17 = 98/traces

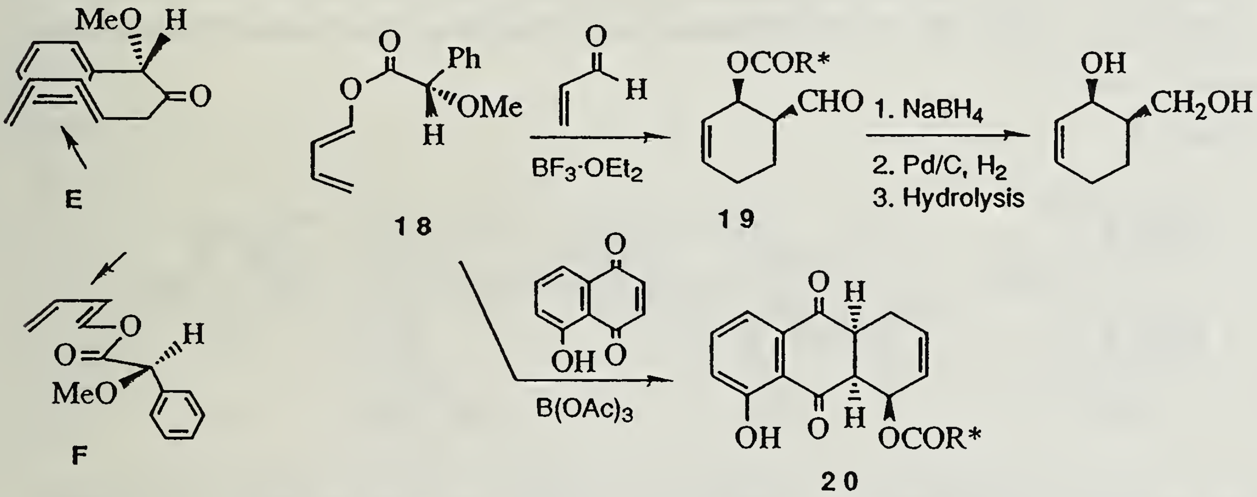
CHIRAL DIENES

Reactions of dienes bearing chiral auxiliary groups have not been so widely studied as those of chiral dienophiles.

1-(*O*-Methylmandeloxy)dienes

Trost et al.[11a] reported the Diels-Alder reaction of 1-(*O*-methylmandeloxy)diene **18** to acrolein in the presence of $BF_3 \cdot OEt_2$, which gave the adduct **19** in 98% yield and 75% de. More significantly, the addition of the diene **18** to juglone in the presence of $B(OAc)_3$ provided the adduct **20** in 98% yield with virtually complete stereoselection. To rationalize this selectivity, initial π-stacking model **E** was revised to the "perpendicular model" **F**,[11b] in which attack of the dienophile on the diene face opposite to the phenyl group should be preferred (Scheme VIII).

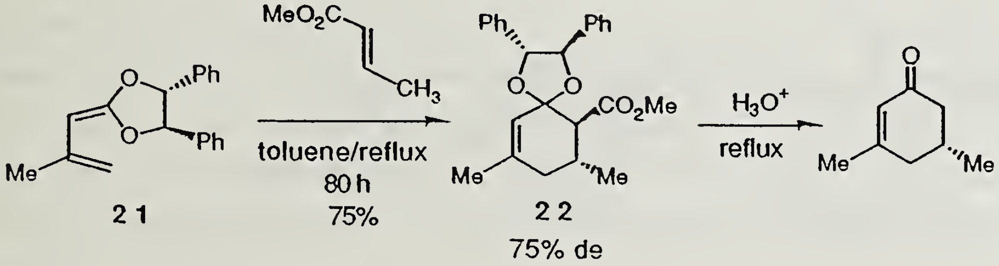
Scheme VIII



Vinyl Ketene Acetals

Konopelski et al.[12] have reported preliminary experiments in the Diels-Alder reaction using enantiomerically pure vinyl ketene acetals derived from α,ß-unsaturated carboxylic acids as chiral dienes as exemplified by Scheme IX.

Scheme IX



A major advantage of this method is that the product of the Diels-Alder reaction is a ketal, fully functional as a protecting group for subsequent synthetic manipulations and/or easily removed to afford a ketone.

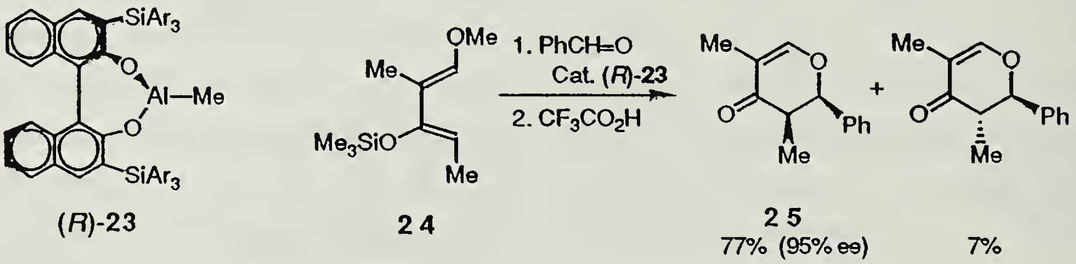
CHIRAL CATALYSTS

After pioneering works on chiral Lewis acids in Diels-Alder reactions by Koga[13] and Danishefsky[14], more precise design of chiral Lewis acids has been performed to achieve high levels of stereoselectivity.

Chiral Organoaluminum Reagents

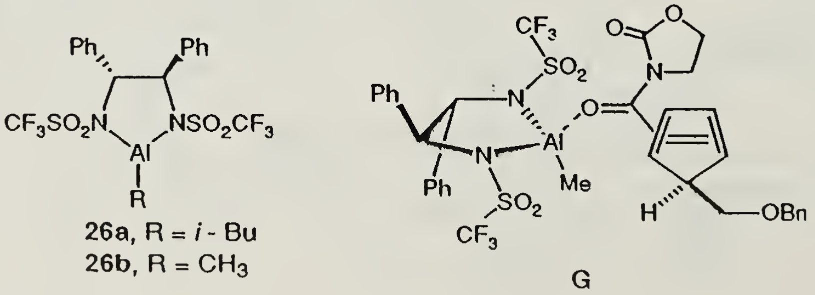
Yamamoto et al.[15] have developed the asymmetric hetero-Diels-Alder reaction by using the chiral organoaluminum catalyst of type (*R*)-**23** and (*S*)-**23** derived from 2,2'-binaphthol . The reaction of the siloxydiene **24** with benzaldehyde in the presence of (*R*)-**23** and subsequent treatment of the adduct with CF_3CO_2H afforded the *cis*-dihydropyrone **25** with 77% yield with 95% ee (Scheme X).

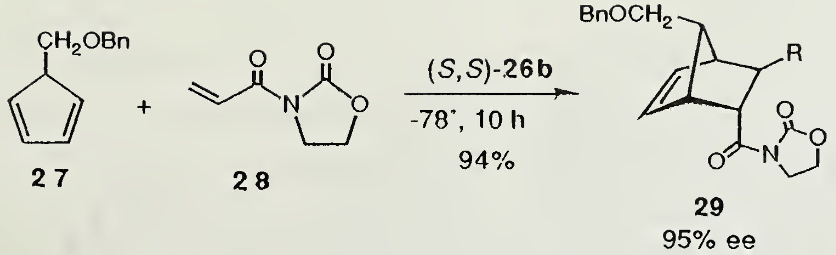
Scheme X



Corey et al.[16] have described a new, highly practical, chiral controller system, (±)-1,2-diamino-1,2-diphenylethane . The reaction of **28** and the cyclopentadiene **27** in the presence of (*S*,*S*)-**26b** as catalyst afforded **29** in 94% yield and 95% ee. The absolute stereopreference in this reaction to form **29** seems to be the result of catalyst binding to acryloyl carbonyl of **28** at the lone pair anti to nitrogen, fixing the acryloyl group in the *s-trans* conformation, as shown in G of Scheme XI.

Scheme XI

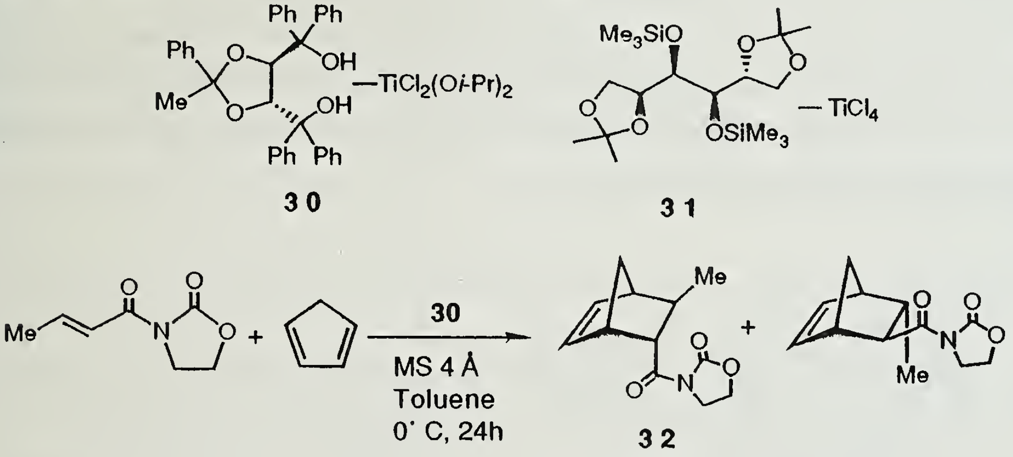




Chiral Organotitanium Reagents

Narasaka[17] and Chapuis[18] have developed a highly enantioselective Diels-Alder reaction by employing chiral titanium reagents **30** and **31** generated in situ from $TiCl_2(O\textit{i}\text{-}Pr)_2$ and the chiral diol derived from tartaric acid, and from $TiCl_4$ and the chiral silyl ether, respectively. For example, with a catalytic amount of the titanium reagent **30**, reaction of 3-crotonyl oxazolidin-2-one with cyclopentadiene in the presence of 4 Å molecular sieves afforded the endo adduct **32** in 91% ee (Scheme XII).

Scheme XII

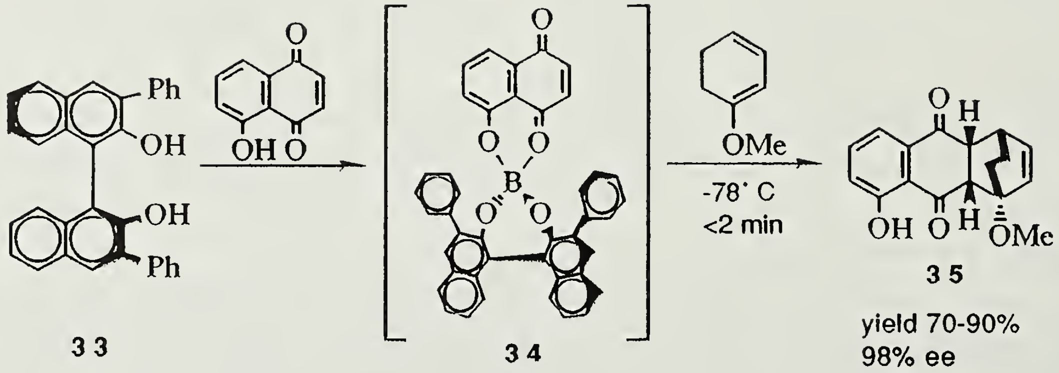


yield 87% (endo/exo = 92/8)
endo ee = 91%

Chiral Organoboron Reagents

Kelly[19a] and Yamamoto[19b] have independently developed the asymmetric Diels-Alder reaction of naphthoquinone derivative and diene in the presence of chiral boron reagents derived from 2,2'-binaphthol and tartaric acid diamide, respectively. The reaction of **33** via a proposed complex **34** with 1-methoxycyclo-hexa-1,3-diene afforded the adduct **35** in high yield with >98% ee (Scheme XIII).

Scheme XIII



33

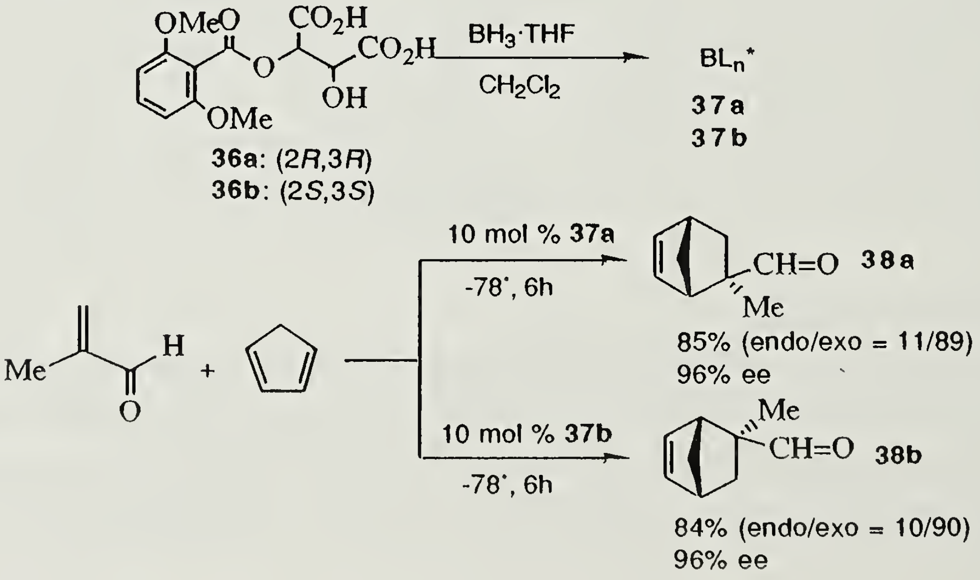
34

35

yield 70-90%
98% ee

Yamamoto et al.[20] have discovered that chiral (acyloxy)borane (CAB) complexes derived from tartaric acid and borane catalyze the Diels-Alder reactions of α,ß-unsaturated aldehydes to bring about remarkable asymmetric induction in a highly catalytic fashion. The Diels-Alder reaction of methacrolein and cyclopentadiene in the presence of the CAB complex **37a** and **37b** afforded the exo cycloadduct **38a** and **38b**, respectively, with high enantioselectivity (Scheme XIV). This process was found to be quite general and be applicable to various dienes and aldehydes with high enantioselectivity. The mechanism of asymmetric induction is not clear, but it was supposed that the α-hydroxy acid and borane might form a five-membered ring structure, and the remaining carboxyl group might not bond to the boron atom.

Scheme XIV



36a: (2*R*,3*R*)
36b: (2*S*,3*S*)

37a
37b

38a
85% (endo/exo = 11/89)
96% ee

38b
84% (endo/exo = 10/90)
96% ee

CONCLUSION

The asymmetric Diels-Alder reaction has been established as one of the most powerful tools for the synthesis of enantiomerically pure compounds. Almost complete asymmetric induction has been achieved by using dienophiles bearing recoverable chiral auxiliaries. Although chiral diene auxiliaries have not shown as good selectivity as chiral dienophiles, they are still of considerable interest. The necessity of the process for introduction and subsequent removal of chiral auxiliaries limits the practical application of chiral diene or dienophile auxiliaries. Chiral Lewis acid catalysts have been found to be very effective to circumvent this limitation. So far they have shown great promise and the development of new chiral catalysts for asymmetric induction will continue to be an area of intense activity.

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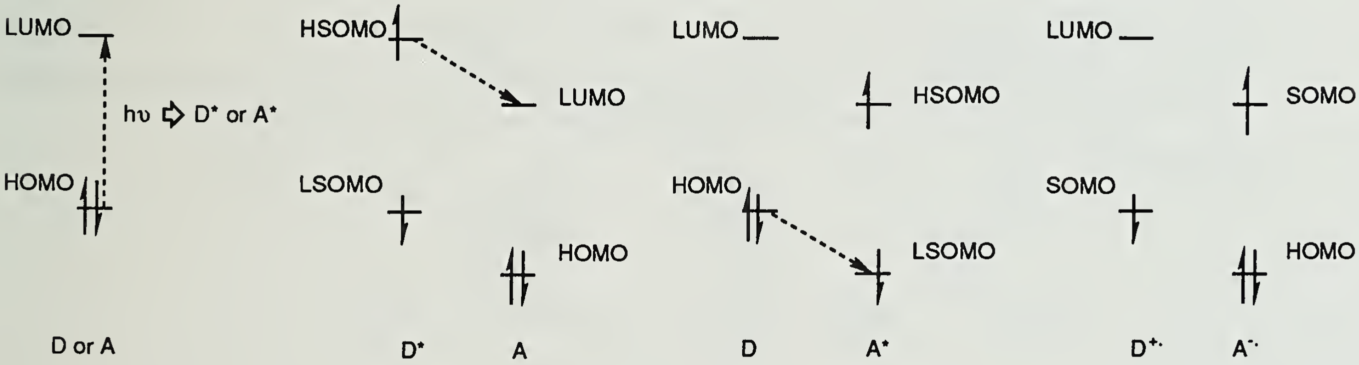
TWISTED INTRAMOLECULAR CHARGE TRANSFER (TICT) STATES: THEORY AND APPLICATIONS

Reported by Samantha Chan October 12, 1989

INTRODUCTION

Charge separation is important for many biological and chemical processes including the activity of flavin mononucleotides and photosynthesis.[1] Charge separation can be accomplished in several ways, for example by charge transfer. Charge transfer occurs when an electron rich donor provides a partial to full electron to an electron poor acceptor in the ground state.[2] A charge transfer complex would form and would be held together through Coulombic forces. Another way to achieve charge transfer is through photoinduced electron transfer between an electron rich donor and an electron poor acceptor to form a radical cation and a radical anion (Scheme I). An excited donor will have a single electron in each of the former HOMO and LUMO of its ground state. The former HOMO and LUMO become the LSOMO or lowest singly occupied molecular orbital and HSOMO or highest singly occupied molecular orbital, respectively. Electron transfer occurs when the electron in the HSOMO of the ground state donor is transferred to the lower lying LUMO of the acceptor. An excited acceptor will have an electron in what was the HOMO and LUMO of its ground state, and electron transfer will occur when one of the electrons of the HOMO of the donor is transferred to LSOMO of the ground state acceptor. A radical cation and radical anion can also be formed when transfer of a full charge between an electron donor and acceptor occurs. A full intramolecular charge transfer from the donor to the acceptor of the same molecule leads to a species which sometimes exhibits a "unique" dual fluorescence. This abstract will address the "unique" fluorescence of the donor-acceptor system of 4-dimethylaminobenzonitrile (DMABN)(**1**) and some possible applications which utilize this photophysical property.

Scheme I



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BACKROUND

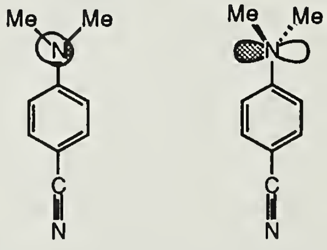
In 1954, Lippert et. al.[3] discovered the dual fluorescence of DMABN(**1**) in polar solvents. They found a short wavelength fluorescence band characteristic of many benzene derivatives as well as an anomalous longer wavelength band. Normally, a molecule only exhibits one fluorescence band. A molecule may be excited to a more energetic level than the first excited state singlet but will undergo a very rapid non-radiative transition to the first excited state singlet. This first excited state singlet will then undergo a radiative transition to the ground state and would be the source of the single fluorescence band.

To explain the dual fluorescence of DMABN, Lippert postulated that the second excited state was more polar than the first excited state; polar solvent reorganization would stabilize the second excited state to an energy level lower than the first. The transition from the lowered second excited state to the ground state would lead to the longer wavelength, anomalous fluorescence in competition with the normal fluorescence from the first excited singlet state.

In 1973, Rotkiewicz, Gellmann, and Grabowski [4] disproved Lippert's theory. They reasoned that if the two fluorescence bands were from two different singlet to ground state transitions, the difference in orbital symmetry of the two singlet states should lead to emissions which were perpendicularly polarized. Instead they found that the emissions were parallel. This suggested that the two emissions arose from the same singlet excited state.

Grabowski et. al.[4] then proposed that the origin of the dual fluorescence was two excited rotamers of DMABN (Scheme II). The normal fluorescence occurred when the p–orbital of the amino nitrogen was perpendicular to the plane of the phenyl ring (**1a**). The anomalous fluorescence was attributed to the rotamer where the p-orbital of the amino nitrogen was parallel with the plane of the phenyl ring (**1b**). It was also proposed that in rotamer (**1b**) a full charge transfer from the amino nitrogen to the cyano group had occurred leading to a highly polar molecule. Thus, solvation by polar solvent lowers the energy of this excited state. This lower energy singlet was thought to be the source of the low energy band. This state has come to be known as the *twisted intramolecular charge transfer* state (TICT).[5,6,7]

Scheme II

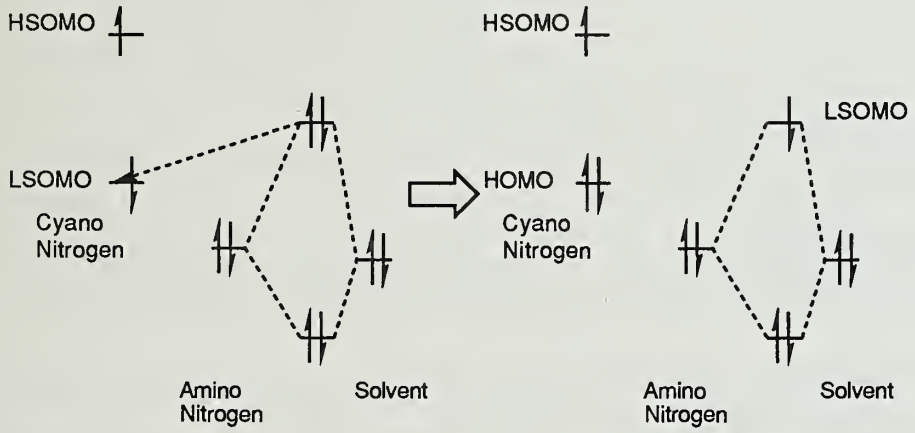


(1a) (1b)

A CHALLENGE TO THE TICT STATE THEORY

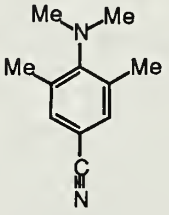
Another explanation for the observed dual fluorescence which questioned the validity of the TICT state theory was the solute-solvent exciplex theory proposed by Visser and Varma in 1980.[8] They suggested that an excited state solute molecule would complex with a solvent molecule through orbital interactions between the amino group of the solute and the solvent. The emitting species would be the exciplex. In the case of DMABN(**1**), the lone pair electrons of the amino nitrogen would interact with the lone pair electrons of a polar solvent such as acetonitrile to form both a bonding and antibonding orbital. If the solute were excited, the HOMO and LUMO of the benzonitrile component would contain one electron each. If this LSOMO had an energy lower than that of the newly formed antibonding orbital, a more energetically favored complex would form if an electron from the antibonding orbital entered the LSOMO level. This must be the driving force for the formation of the exciplex since the initial interaction between two filled orbitals would lead to a destabilized state with antibonding character. This is the exciplex binding scheme that Visser and Varma have proposed (Scheme III).[8,9] It was this exciplex which was the source of the anomalous fluorescence. To test for this proposal, a series of experiments were performed which included quenching studies[8], model studies[8,9] and picosecond laser spectrospcopy.[10]

Scheme III

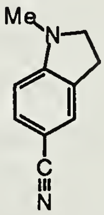


Visser and Varma did a series of experiments where the fluorescence of DMABN was quenched with a variety of polar solvents.[8] They found that the ratio of the intensities of the anomalous fluorescence to normal fluorescence was directly proportional to the concentration of the polar solvent. Also, the quenching experiments showed a linear Stern-Volmer plot. These experiments suggested the formation of a 1:1 complex between an excited solute and an solvent molecule known as an exciplex.

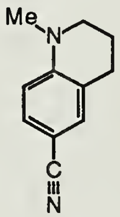
Visser and Varma also studied a variety of model compounds to find more evidence for exciplex emission.[8,9,10,11] In studying the fluorescence of 3,5-dimethyl-4-N,N-dimethylamino-



(2)



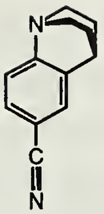
(3)



(4)

benzonitrile (TMABN) **(2)**[8], which has its dimethylamino group rotated out of the plane of the phenyl ring, it was found that TMABN had only a single band of fluorescence in both polar and nonpolar solvents. It was noted that the band was slightly attenuated and blue shifted in a nonpolar solvent with a small amount of polar solvent. This led Visser and Varma to conclude the band was a superposition of two components; the originally excited molecule and the exciplex. The rate of formation of exciplexes was then inferrred to be related to the angle between the dimethylamino group and the phenyl ring. First, from the rates of quenching of the TMABN vs. DMABN, it appears that the TMABN forms exciplexes more easily than the DMABN. Next, when the C-N bond between the phenyl ring and the amino group was restricted so that the lone pair orbital on the nitrogen had to be parallel to the π-orbitals of the phenyl ring as in compounds **3** and **4**, there appeared to be no exciplex emission nor quenching by a polar solvent. It was then suggested that the exciplex may be stabilized through the conformation of the solute. Namely, a twisted state of the solute was thought to favor the exciplex formation and would explain the difference in the rate of quenching between the TMABN and the DMABN. Because of this interpretation, Visser and Varma then modified their theory to include a twisted solute exciplex and a planar solute exciplex and attribute the anomalous fluorescence of both the TMABN and DMABN to the twisted solute exciplex.[8]

The TICT state theory suggested a different interpretation of the model study experiments.[5] Since the dual fluorescence was due to two different rotamers of the molecule, the TMABN exhibited only one fluorescence band because the dimethylamino group is restricted to be out of the plane of the phenyl ring. Compounds **3** and **4** are resticted to have their nitrogen planar and can therefore only exhibit one fluorescence band; they cannot exhibit the twisted intramolecular charge transfer band. One other compound which was studied was 6-cyanobenquinodidine **5** where the lone pair of the nitrogen was restricted to be in the plane of the phenyl ring.[12] This compound had only one fluorescence band at 470 nm in MeOH which was attributed to the TICT state.



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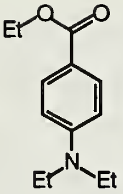

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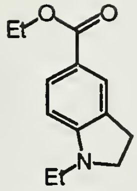


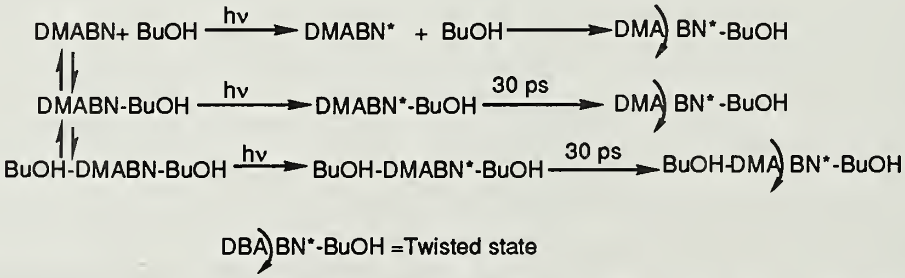
(7)

Another piece of evidence which supports the TICT state model is work done by Rotkiewicz and Rubaszewska.[13] They found the TICT fluorescence of TMABN in the gaseous phase where exciplex formation cannot occur. In both nonpolar and polar solvents, only one fluorescence band is observed for TMABN. The band is shifted to longer wavelengths in polar solvents. This is attributed to the TICT state because the dimethylamino group is restricted to be at least 60° out of the plane of the phenyl ring. In the vapor phase, TMABN exhibited one fluorescence band at a wavelength similar to that observed in nonpolar solvents. This, too, was attributed to the TICT state fluorescence. Rotkiewicz and Rubaszewska do not discount any of the prior observed solvent effects; in fact, they find a correlation between the electron affinity of the solvent and the solvent shifts of the fluorescence band.[13] This does indicate that complexes may exist, but the fluorescing compound is in a TICT state regardless of the solvent interaction, as demonstrated by the TICT state fluorescence in the gaseous state.

Another condition where the exciplex could not be formed was in an inert solvent such as a saturated hydrocarbon which has no lone pair electrons. Wermuth, Rettig and Lippert[14] made a comparison of the fluorescence specta of **6** and **7** in the inert solvent system n-pentane/2,2-dimethylbutane (3:8). It was found that **6** exhibited dual fluorescence while **7** did not. The anomalous fluorscence for **7** is not allowed due to the nitrogen being restricted to lie in the plane of the phenyl ring. In a mixture of methylcyclohexane/methylcyclopentane (1:1), dual fluorescence for **6** was again noted, and it was temperature dependent. At lower temperatures, the normal fluorescence increased in quantum yield. Presumably the lower temperatures increased the viscosity which hindered the rotation required for anomalous fluorescence. It was also found that lowering the temperature also shifted the anomalous fluorescence to lower energy. This can be explained in terms of solvent effects and may explain how solvent can help stabilize the TICT state. The solvent molecules will have induced polarity. At lower temperatures, the solvent can move closer to the excited state molecule stabilizing the polar TICT state. It seems surprising that an induced dipole in nonpolar solvent can cause relaxation of (**6**) to the TICT state since the closely related DMABN does not exhibit a TICT state fluorescence in nonpolar solvent. In fact, Visser and Varma attempted to duplicate the results and were not successful.[15]

In an effort to distinguish between the solute-solvent exciplex theory and the TICT state model, Wang and Eisenthal[16] performed picosecond fluorescence spectrospcopy experiments to study the effect of solvent on the dual fluorescence of DMABN. They excited the DMABN in butanol/hexadecane solutions at 264 nm and monitored the fluorescence decay at 350 nm of the normal band and fluorescence rise at 470 nm of the anomalous band. In a pure butanol solution, it was found that the rise time for the fluorescence at 470 nm was 30 ps. In the butanol/hexadecane solutions, two components of both the rise and decay curves were found. The fast component was independent of temperature, and its rise time remained at 30 ps although the magnitude of the fast component decreased with decreasing butanol concentrations. The slow component rises at a rate which was directly proportional to butanol concentration; the equations shown in Scheme IV were proposed to explain this data. The DMABN and solvent are in equilibrium with DMABN-solvent complexes where the complex can contain more than one solvent molecule. After excitation of the DMABN, the DMABN-S complex or S-DMABN-S complex will relax to the twisted state in 30 ps. An uncomplexed, excited DMABN will need to be complexed with a solvent molecule before it can relax to the twisted state. It is thought that a DMABN-S complex is necessary for the stabilization of the twisted solute. This is the step dependent on butanol concentration and is the source of the slow component of both the rise and decay curves of DMABN in butanol/hexadecane solutions. Although Wang and Eisenthal feel this evidence suppports the TICT state model because they found a 1:1 complex does not necessarily form, these results seem to fall half-way between the TICT state model and the solute-solvent exciplex model. The results support Visser and Varma's revised proposal that the exciplex can contain a twisted species; however, they can also be consistent with the TICT state theory if stabilization of a solute such as DMABN is necessary for the formation of the TICT state.

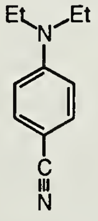
Scheme IV



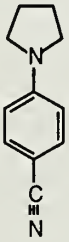
Another study of solvent effects on the fluorescence of DMABN was done by Suppan.[17] He observed a dual fluorescence for DMABN in 1-fluoropentane and only a single fluorescence in perfluorohexane. Exciplex formation is expected to be more likely for DMABN in perfluorohexane with fourteen times more lone pair electrons available than 1-fluoropentane, yet this does not seem to be the case as shown by the single component fluorescence. If DMABN does not exhibit an exciplex emission in perfluorohexane, then it is likely that 1-fluoropentane which has only three lone pairs of electrons will not either. Since DMABN did exhibit dual fluorescence in 1-fluoropentane, Suppan reasoned that 1-fluoropentane stabilized the TICT state through dielectric stabilization rather than exciplex formation because 1-fluoropentane has a larger dielectric constant than perfluorohexane.

FURTHER EVIDENCE FOR THE TICT STATE

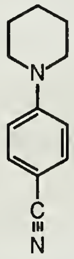
A series of experiments reported by Rettig[18] support the idea that rotation occurs when the anomalous fluorescence is observed. The alkyl groups of the amine were varied to alter the relative size of the rotating species. The molecules **8-11** were used in this study. Rettig postulated that in the same solvent, TICT formation would be hindered for a molecule with a larger rotating volume. Comparison of **10** and **11** at low temperatures demonstrated that the larger volume of the substituted piperidino group on compound **11** hindered TICT formation. The relative intensity of the anomalous fluorescence to that of the normal fluorescence was smaller for **10** indicating that rotation is necessary for TICT formation. Both **8** and **10** have flexible amino groups. The piperidino ring of **10** can exist in a number of possible confomations. The two ethyl groups on the amine of **8** can fold or unfold and are free to rotate like propellers. Work done by Hu and Zwanzig[19] suggested that **8** would have an effective larger rotating body than **10** because of an increase in friction due to the "propellers" of **8**. A comparison of the rate of formation of the TICT state for both **10** and **8** show the rate for **10** to be larger than that of **8**. This is what was predicted due to the larger effective rotating volume of **8**. Compound **9** contains a pyrrolidino ring which is slightly strained making it almost planar. Due to the possible conformations of the piperidino ring in **10**, the lone pair orbital of the nitrogen can rotate out of the plane through these conformations without actually having to rotate about the C-N bond. The effective rotating volume of **10** will be smaller than that of **9** since it should need to rotate less to reach the TICT state. This is shown by the larger rate of formation of the TICT state for **10** than for **9**. Though the results of this experiment were offered as evidence for the existance of the TICT state model, they can also support the solute-solvent exciplex system if the fluorescing exciplex does indeed contain a twisted solute molecule.



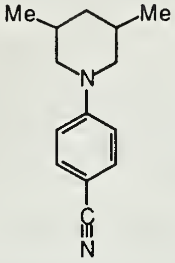
(8)



(9)



(10)



(11)

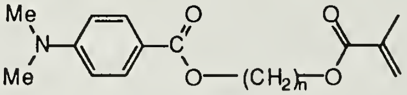
The proposed TICT state theory suggests that the TICT state can be thought of in terms of a radical cation bonded to a radical anion. The absorption of this polar state should lead to the sum of the absorption of the radical cation and the radical anion. With this in mind, Okada, Mataga, and Baumann[20] used picosecond laser photolysis to study the transient absorption of DMABN and TMABN. The transient absorption of both in acetonitrile gave a band very close to that of the benzonitrile anion radical. Grabowski[21] used the same technique to look at 4-dimethylamino-benzaldehyde(DMABA) and found evidence for the benzaldehyde radical anion which is expected to result from the TICT state of DMABA. In both cases, evidence for the radical anion is found which is a good indication that a complete charge transfer has occurred between the donor and acceptor.

APPLICATIONS OF TICT STATE MOLECULES

Molecular Probes.

Cyclodextrins possess a hydrophobic cavity which can complex aromatic molecules. This may serve as a model for enzyme-substrate complexes.DMABN has been used to study the environment of the cavity and the location of the probe inside the cavity. The TICT compound DMABN is used for several reasons. The long wavelength emission is only observed in polar solvents and would not be expected to emit if totally enclosed in the cyclodextrin cavity.[22,23] Rotation around the phenyl-nitrogen bond will be hindered inside the cavity. If the probe were only partially in the cavity, perhaps the fluorescence could give an indication as to the degree. Next, the molecule is relatively small compared to other common aromatic probes such as pyrene and should perturb the cavity to a lesser degree than pyrene. In this way the actual complexation could be studied rather than any manisfestation due to deformation of the cavity by the pyrene probe. Some early work done by Turro et. al.[23] demonstrated that the α–cyclodextrin-DMABN complex had a larger effect on the enhanced emission than any of the other types of cyclodextrins. They also found the environmental polarity experienced by DMABN was the same as if it had been in a solution of butanol. The polarity of butanol falls about half-way between dichloromethane and water.

The morphology of polymers have also been probed with TICT state compounds. For example, **13** was prepared and copolymerized with methyl methacrylate to produce the polymer to



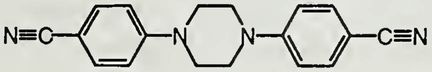
n=2,4,8,12

(13)

be studied. The TICT compound dimethylaminobenzoate will then be chemically bound to the polymer. This method is preferable to adding the TICT compounds to a solution of the polymer to be studied.[24] The advantages to this method are that one is not guessing as to the location of the binding site of the probe or the where the probe will locate when added to the polymeric solutions. Work done by Hayashi and Tazuke[24] the TICT emission of the bound dimethylaminobenzoate to be affected by local viscosity and polarity. This makes the dimethylaminobenzoate a good fluorescent probe for the study of the local environment in a polymer. For instance, Hayashi and Tazuke[25] use this probe to study the mobility of side chains on the main polymer chain. A variety of methyl methacrylate monomers of varying length with the bound dimethylaminobenzoate were copolymerized with a large excess of methyl methacrylate so that the TICT compound was present at less than 0.04% weight. It was found that the TICT emission decreased when the side chain length was shorter. The rotation necessary for the TICT state is hindered; this indicates that side chain motion is restricted by the main polymer chain.

Molecular Switches.

Molecules which can mimic some of the processes needed for electronic devices is a topic of great interest. The switching process is one of the most important since it is necessary for computation. The ideal molecular switch should undergo electron transfer to create a highly polarized system which is conductive, but it should be possible to turn this process on or off. Launay et al.[26] proposed that N,N'-bis(4-cyanophenyl)piperazine (12) might make a good switch.The two cyanophenyl groups are parallel though not in the same plane. The compound does demonstrate TICT emission although it is not known whether one or both cyanophenyl groups rotate. The rotation of one of the cyanophenyl groups would lead to complete orbital decoupling. This could be the on/off mechanism of the switch. This work is recent and there are still some problems to be solved. All the studies are done in solution rather than in the solid state condition required for a switch.



(12)

CONCLUSION

Dimethylaminobenzonitrile and many of its analogs exhibit a dual fluorescence which was attributed to a twisted intramolecular charge transfer state. While there is good evidence that the TICT state exists, it is still uncertain of the exact role solvent plays in its formation. More experiments are needed to elucidate solvent influence. Nevertheless, the dual fluorescence of these compounds has been used to study polymers, micelles, and cyclodextrins. These TICT compounds may also find applications in electronics in the near future.

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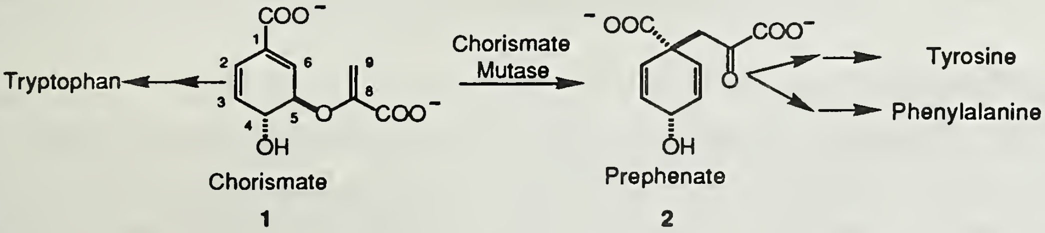
THE MECHANISM OF ACTION OF CHORISMATE MUTASE

Reported by Kurt W. Saionz November 9, 1989

INTRODUCTION

The [3,3]-sigmatropic (Claisen) rearrangement of chorismate (**1**) to prephenate (**2**) is at the branchpoint of the shikimic acid pathway.[1] This biologically important pathway produces essential aromatic amino acids and a number of other aromatic products in plants and bacteria. (Scheme I).[1] The key enzyme in the shikimate pathway for production of tyrosine and phenylalanine is chorismate mutase which catalyzes the rearrangement of chorismate to prephenate. Chorismate (**1**) is also converted to anthranilate, a precursor to the amino acid trytophan.

Scheme I



The enzyme catalyzed rearrangement of chorismate is of interest for a number of reasons, primarily, that it is the only apparently pericyclic reaction in primary metabolism catalyzed by an enzyme.[2] Secondly, because the reaction takes place both enzymatically and non-enzymatically, a greater understanding of the enzymic reaction can be achieved by comparing the two processes. The rearrangement occurs non-enzymatically with a half-life of 15.7 h at 30 °C at pH 7.5. Chorismate mutase accelerates this rearrangement by a factor of 1.9×10^6.[3,4] Finally, the inhibition of the chorismate mutase could be exploited in the design of powerful herbicides or antimicrobial agents since this rearrangement is essential for production of aromatic amino acids in plants and bacteria.

Previously, Martha Schlicher presented a University of Illinois student seminar on the biosynthesis of chorismate (**1**) and the probable transition state for the sigmatropic rearrangement which it undergoes.[1a] In this paper, six possible mechanisms of action for the chorismate mutase enzyme will be presented. Additionally, information about the active site of the enzyme provided by substrate analogs, inhibitors and catalytic antibodies will be discussed.

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NON-ENZYMIC REARRANGEMENT OF CHORISMATE

Structural Effects on the Rearrangement of Chorismate

A number of researchers have investigated the Claisen rearrangement of allyl vinyl ethers which are structurally similar to chorismate.[5-11] Gajewski and coworkers have prepared a number of structural analogs of chorismate and compared their rearrangement rates to determine the contribution of each functional group (Figure 1).[11] The carboxyl group at C-(8) and the Δ^{2-3} double bond were found to cause the largest rate enhancements.

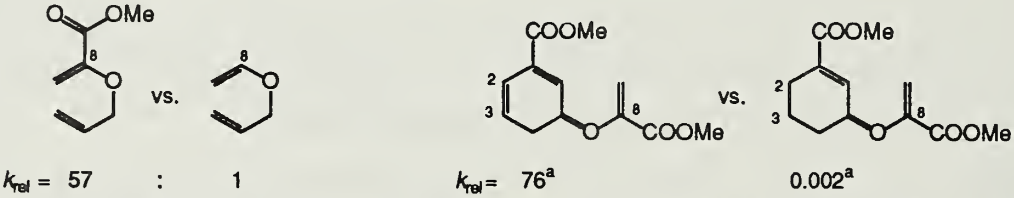


Figure 1. Examples of the structural analogs used by Gajewski. [a] Rates relative to chorismate.

Probable Transition States for the Rearrangement of Chorismate

The two extremes for the transition state of the rearrangement of the parent allyl vinyl ether are shown in Figure 2. Secondary isotope effects have shown that the transition state appeared early on the reaction coordinate and therefore closer in identity to the biradicoloid A than to the diradical species B.[9] In contrast, a dipolar transition state like A' has been proposed for chorismate and similar systems based on solvent (Table I) and substituent effects.[6,11,12] At the present time, the question of whether the non-enzymic transition state is radical or dipolar has not been answered.

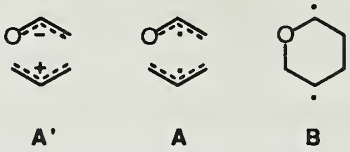


Figure 2. Limiting transition states for the Claisen Rearrangement.

POSSIBLE ENZYME MECHANISMS

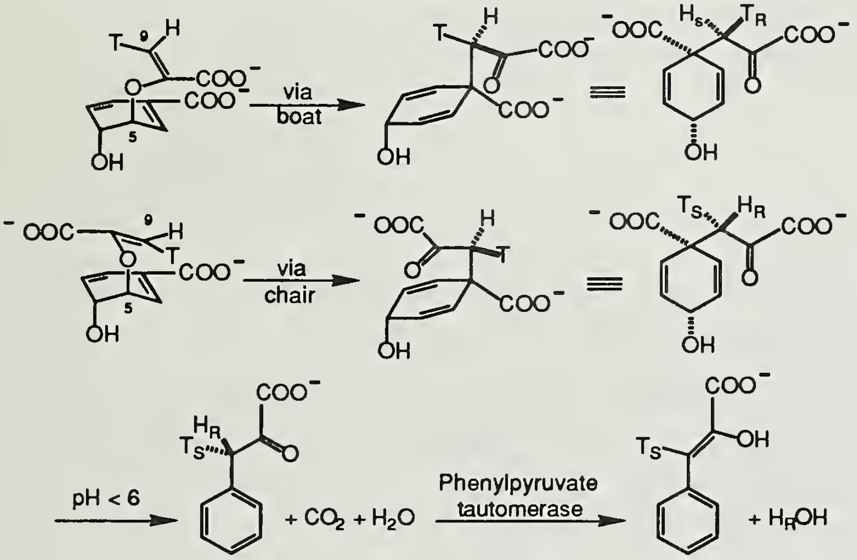
Chorismate Mutase as an Entropy Trap

One of the first mechanistic proposals for chorismate mutase suggested that the enzyme acts as an entropy trap by freezing out degrees of rotational freedom in the ground state of the substrate.[13] The substrate could then proceed to the transition state with a smaller loss in entropy, thereby increasing the reaction rate. Andrews has calculated an enthalpy of activation of 20.71 ± 0.35 kcal/ mol and an entropy of activation of -12.85 ± 0.42 eu for the non-enzymic process.[4] In contrast, the enthalpy of activation for the enzyme catalyzed route is 14.5 kcal ± 0.4 while the entropy of activation has been calculated to be 1 eu.[14] If the enzyme were merely an entropy trap, the corresponding rate enhancement should be 10^3 not the 1.9×10^6 enhancement which is observed. Therefore, Andrews has concluded that the enzyme is not solely an entropy trap but must lower the activation enthalpy as well as the activation entropy of this process.[4]

Transition State Conformation for the Rearrangement of Chorismate

The transition state for the rearrangement of chorismate was assumed to resemble a chair conformation based on calculations which showed it to be more stable than the boat conformation by 2 kcal/mol.[15] The chair conformation was further supported by experiments using stereospecifically labelled *E* and *Z*-[9-^{3}H]- chorismate. The non-enzymic reaction[16]and *in vitro*[1a,17] enzymic reaction showed that less tritium label was lost to solvent by the *E*-labelled chorismate than the *Z*-labelled chorismate indicating that the conformation for rearrangement is chair in both cases (Scheme II). The chair conformation was confirmed *in vivo* by the degradation of tyrosine to determine the position of the label.[1a,18] The mechanistic proposals explored in this paper were based on the assumption that the chair conformation was correct.

Scheme II

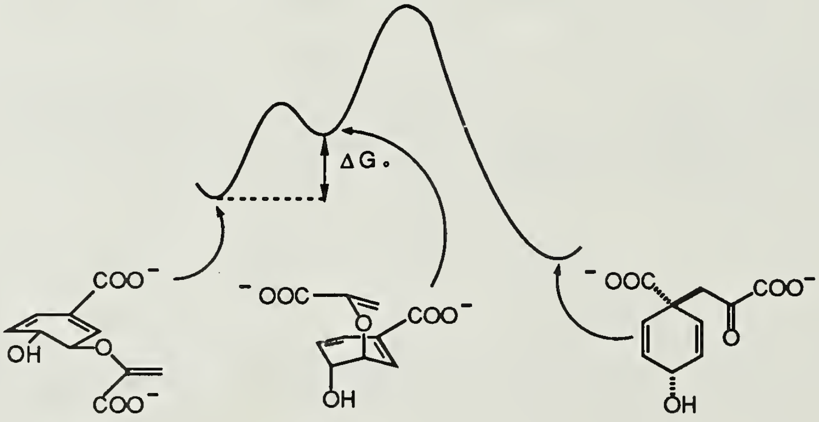


Selective Binding of the Pseudodiaxial Conformation of Chorismate

The concertedness of the chorismate rearrangement, both enzymatically and non-enzymatically, has been probed with secondary tritium isotope effect experiments.[19] Chorismate was labelled at the C-(9) and C-(5) positions of chorismate with tritium using enzymes of the shikimate pathway. The results for the non-enzymic case show that a significant amount of bond breaking is present in the non-enzymatic transition state while there is relatively no bond making. No kinetic isotope effect was observed for the enzymic reaction.

The lack of a secondary kinetic isotopic effect in the enzymic reaction suggests that the rate determining step occurs before the isotopically sensitive rearrangement. This evidence led to the proposal of two mechanisms involving the selective binding of one conformation of chorismate.[19] The first mechanism involves binding of the more stable pseudodiequatorial form (**3**) with a calculated rate constant of 10^5 $M^{-1}sec^{-1}$. The enzyme-substrate complex changes conformation to give an enzyme-pseudodiaxial conformation complex which would then rearrange and dissociate. The observed k_{cat}= 25 sec^{-1} could account either for the conformational change or the rearrangement. The second mechanism proposes that the rate determining step is the binding of the less abundant pseudodiaxial conformer followed by facile rearrangement to prephenate. The "on rate" (k_{on}) of this substrate would be diffusion controlled with a rate of 10^9 $M^{-1}sec^{-1}$.[19] The k_{cat} of 25 sec^{-1} and K_m of 60 µM calculated for chorismate mutase can be used to calculate a pseudodiaxial conformer equilibrium population of one in 2 x 10^6. This is consistent with the value predicted by Andrews using Hückel molecular orbital theory but not with experimental data (*vide infra*).[4]

An energy diagram for the conformational equilibrium of chorismate is shown in Figure 3. The magnitude of ΔG_0 determines the equilibrium between the two conformers of chorismate and therefore which is selectively bound by chorismate mutase.[12]



3 **4** **2**

Figure 3. Free energy profile for the conformational equilibrium of chorismate and the rearrangement of the pseudodiaxial conformer to prephenate.[12]

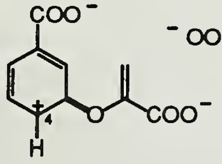
Knowles has used the interrelationship of coupling constants developed by Bowmaker to study the equilibrium of pseudodiaxial to psuedodiequatorial conformations in water and methanol.[12] The results for chorismate, chorismic acid and 4-O-methyl chorismate show that there is a significant amount of the pseudodiaxial conformer in water supporting the selective binding of psuedodiaxial chorismate by the enzyme (Table I).

Table I. Solvent effects and Conformational Equilibrium[12]

Compound	Solvent	k_{H_2O}/k_{MeOH}	% Pseudodiequatorial
Chorismate	H_2O	100	88
Chorismate	MeOH		>98
Chorismic Acid	H_2O	11	83
Chorismic Acid	MeOH		87
4-O-methylchorismate	H_2O	7	60
4-O-methylchorismate	MeOH		65

Mechanisms Based on Electron Deficient Chorismate Intermediates

Electron withdrawing groups are known to expedite [3,3]-sigmatropic rearrangements.[5] Knowles has therefore proposed two mechanisms both involving the introduction of an electron deficient site.[20] In the first case, an acid catalyzed loss of the C-(4) hydroxyl group leaves a cationic species (**5**). In the second case, the formation of an oxiranium species (**6**) is proposed.



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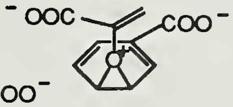


6

12 1.0

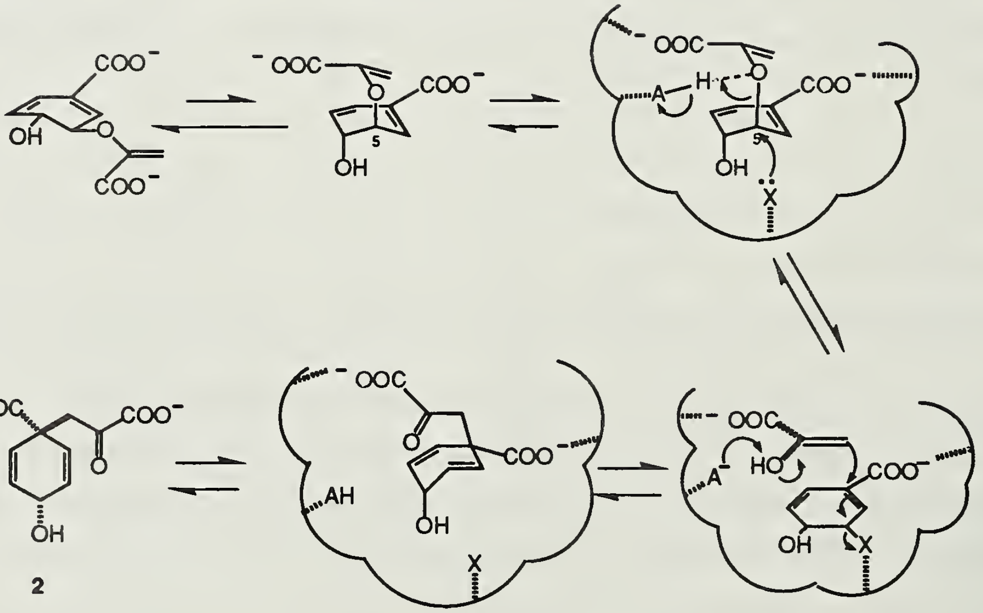
20/21

Tritium labelling at C-4 shows an inverse secondary isotope effect of 0.96 inconsistent with a loss of the hydroxyl group in the rate determining step. Chorismate mutase can catalyze the rearrangement of 4-des-hydroxychorismate (*vide infra*) indicating that the C-(4) hydroxyl group is not necessary for catalysis and thereby negating the C-(4) cation mechanism.[21] The oxiranium intermediate has been disclaimed because it must go through a boat transition state for rearrangement and also because the C-(4) hydroxyl group plays an important role in this mechanism.[20,21]

Nucleophilic Catalysis

Knowles has shown that the deuterium solvent effect for the enzymic reaction is $k_{H_2O}/k_{D_2O} = 2.11 \pm 0.26$.[12] Although the diffusion controlled "on rate" for the psuedodiaxial conformer is expected to be decreased by the less viscous deuterium oxide, the solvent isotope effect is too large to support binding of psuedodiaxial chorismate as the rate determining step. At the present time, the only mechanism which is supported by all the data is that of nucleophilic catalysis (Scheme III).[1b]

Scheme III



Nucleophilic catalysis involves a nucleophilic attack at the C-(5) carbon by a nucleophilic group at the enzyme active site with subsequent breaking of the C-O bond.[20] The resulting enol pyruvate anion then attacks the ring system at C-(1) in an S_N2' fashion. The solvent isotope effect could be explained by general acid-base mediated proton transfers in the enzyme active site. The small inverse isotope effect at C-(4) is ascribed to the slight preference of larger isotopes for the equatorial position shifting the conformational equilibrium towards the pseudodiaxial position, hence, increasing the rate for labelled chorismate.[20,22] The absence of an isotope effect at C-(5) or C-(9) can also be explained by this mechanism because bond making at C-(9) is not the rate limiting step. Also, the C-(5) value of unity for an isotope effect can be explained by a combination of the inverse effect from the conformational change that tritium induces and the normal isotope effect from the nucleophilic attack at this center.[20] Secondary isotope effects at S_N2 centers are usually small and above or below unity depending on the nucleophile and the tightness of the transition state.[23] Currently, nucleophilic catalysis is the most probable mechanism for chorismate mutase.[1b]

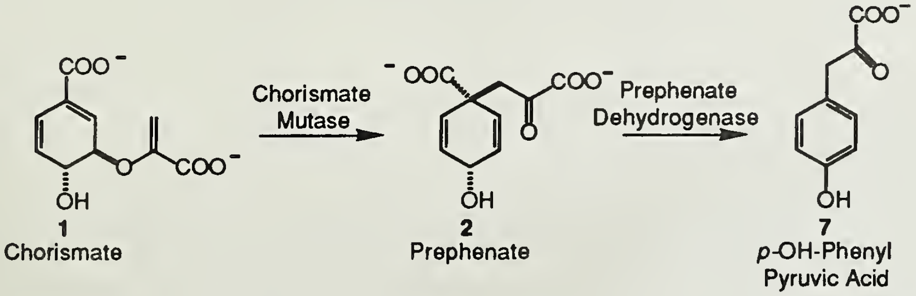
CHORISMATE MUTASE ACTIVE SITE

Knowledge of the active site of chorismate mutase is essential for complete understanding of the mechanistic pathway for the enzyme. The interaction of substrates, inhibitors,and catalytic antibodies with the enzyme can provide this information.

Relationship of the Active Sites in Chorismate Mutase-Prephenate Dehydrogenase

The mechanistic studies above used chorismate mutase-prephenate dehydrogenase isolated from either *Aerobacter aerogenes* or *E. coli*.[24] Two steps in the shikimate pathway to tyrosine are catalyzed by this bifunctional enzyme (Scheme IV). The enzyme is composed of two similar subunits,[25] each of which contain two chemically different sites where chorismate and prephenate can bind. It was shown that the enzyme contains four proximal binding sites by the ability of four molecules of inhibitor to bind to one molecule of enzyme and that each of these inhibitors allosterically increases the ability of the next inhibitor to bind.[26] Certain inhibitors only affect the dehydrogenase portion of the enzyme and not the mutase portion showing that the two sites on each subunit are chemically unique.[24]

Scheme IV



Structural Requirements for Binding

For a complete understanding of the enzyme catalysis reaction, the substrate functionalities which are important for binding and catalysis by chorismate mutase must be ascertained. Berchtold has shown that the des-hydroxy analog (**8**) rearranges faster with a rate increase (k_{cat}/k_{uncat}) of 100 in the presence of the enzyme, indicating that the hydroxyl group at C-(4) is unnecessary for binding and rearrangement in the enzymic reaction.[21] The ring diene, while increasing the rate of the thermal reaction, is not necessary for catalysis by the enzyme as shown by the ability of analog (**9**) to act as a substrate (Figure 4).[27]

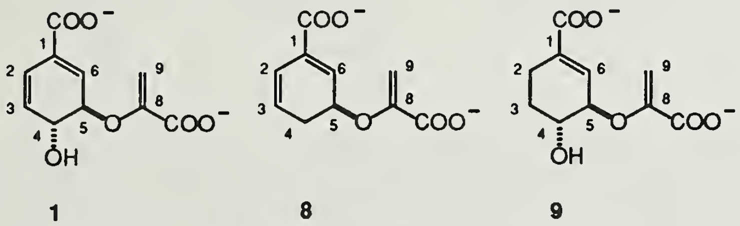
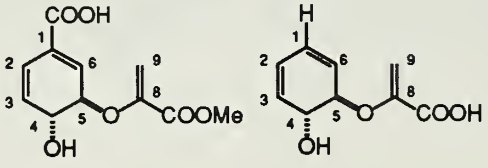


Figure 4. Substrates for chorismate mutase.

Transformation to the C-(8) methyl ester at (**10**) or replacing the C-(1) carboxyl group with hydrogen (**11**), creates analogs which are no longer substrates for chorismate mutase (Figure

5).[21,27] Therefore the two carboxylate groups are the only functionalities on the cyclic allyl vinyl ether system important for catalysis by the enzyme.[21,27]

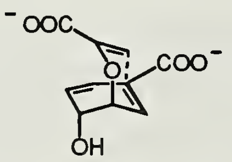


10 **11**

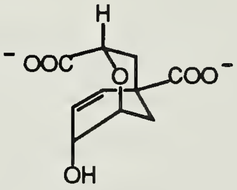
Figure 5. Analogs which are not substrates for chorismate mutase.

Inhibition of Chorismate Mutase

By testing the inhibition of structural analogs of chorismate information concerning the active site of chorismate mutase can be obtained. Inorganic anions were used to show that there are up to two cationic moieties in the chorismate mutase active site.[14] The importance of the side chain oxygen in binding is demonstrated by the increased inhibition by **12**, $I_{50} = 0.26 \pm 0.06$ µM as compared to $I_{50} = 67 \pm 4$ µM for **13**.[28] The I_{50} is the amount of inhibitor necessary for 50% inhibition of the enzyme when the substrate concentration is equal to K_m. Exo analog **14**, a mimic of the chair transition state, is a better inhibitor then its endo counterpart **15** which models the boat transition state supporting the chair conformation for the rearrangement of chorismate.[29]



Chair Transition State



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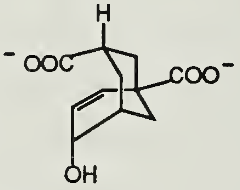

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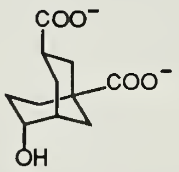

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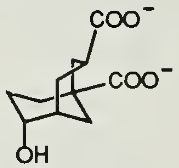

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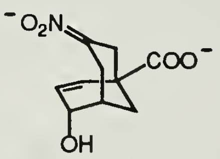

16

The design of many of these structures is based on the idea that the enzyme catalyzes a reaction by stabilizing the transition state, and therefore, the best inhibitors should be those which best mimic the transition state.[28] Interestingly, the inhibitor **16**, which is an excellent mimic, does not bind as well as endo isomer **12** in which the carboxylate is actually in a different position than in the rearrangement transition state.[28] Analog **12** is currently the most effective inhibitor, with a K_i = 0.12 μM as compared to a K_m= 0.34 μM of chorismate itself, however, **12** does not approach the binding enhancement that a transition state analog should have.[28] One reason for this may be that the rearrangement of chorismate is not the rate determining step, which supports the nucleophilic mechanism, or as Andrews suggested, the side chain carboxylate, or other parts of the analogs may not be correctly aligned.[29]

Catalytic Antibodies

Inhibitor **12** attached to keyhole limpet hemocyanin and bovine serum albumin has been used to successfully elicit catalytic antibodies which enhanced the rate of the chorismate to prephenate rearrangement.[30] An antibody against **12** attached to protein by a glutaric acid derivative was found to have a $k_{cat} = 7.2 \times 10^{-2}$ min^{-1} and a K_m = 51 μM at 14 °C at pH 8.[30a,b] This antibody was shown to selectively catalyze the natural (-)-chorismate and not (+)-chorismate by lowering the enthalpy and not the entropy of activation.[30a,b] An antibody elicited against **12** connected to protein by a carbamate-diazonium linkage had a k_{cat} = 2.7 min^{-1} and a K_m = 260 μM at 10°C at pH 7.[30c] The increased rate due to the antibody was k_{cat}/k_{uncat} of 10^4 comparable to the k_{cat}/k_{uncat} of 3×10^6 under similar conditions for chorismate mutase. Chorismate reacts in the induced binding pocket in these antibodies as shown by the ability of **12** to successfully inhibit the antibodies.[30] The antibody, like the enzyme, requires that the substrate have two carboxylate groups for catalysis as shown by the inability of the dimethyl ester of chorismate to act as a substrate.[30c] Because there was no deuterium solvent isotope effect for the antibody catalyzed reaction, the antibody is thought to have a different mechanism than the enzyme.[30c]

CONCLUSION

Currently, the nucleophilic catalysis mechanism is most consistent with existing data. More work needs to be done in confirming the mechanism used in both the antibodies and the enzyme. Also, an inhibitor and chemical model for the enzyme should be designed which are consistent with the nucleophilic enzyme mechanism.

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MECHANISTIC STUDIES ON THE OXIDATION OF ALCOHOLS BY RUTHENIUM COMPLEXES

Reported by Naijie Zhang November 13, 1989

INTRODUCTION

Ruthenium complexes can be used to catalyze the oxidation of alcohols. Sharpless et al. have found that the combination of a $RuCl_2(PPh_3)_3$ with an amine-N-oxide was effective for the oxidation of alcohols.[1] Very recently, Oshima et al. have found that primary alcohols are oxidized much faster than secondary alcohols with $RuCl_2(PPh_3)_3/Me_3SiOOSiMe_3$ system.[2] Ruthenium tetroxide is well established as a strong and effective oxidant for the conversion of secondary alcohols to ketones.[3] This reagent is especially effective for the oxidation of carbohydrates[4] and steroidal alcohols[5] to corresponding ketones in good yields. The reactions with RuO_4 can be performed by using a catalytic amount of RuO_2 or $RuCl_3$ in combination with secondary oxidants such as $NaIO_4$, NaOCl, or $NaBrO_3$.[6] Recently, the ruthenate (RuO_4^{2-})[7] and perruthenate (RuO_4^-)[8] anions have been found to be more effective in the selective oxidation of alcohols. However, few mechanistic details of the oxidation of alcohols by oxo ruthenium complexes are known. In this paper, detailed kinetic and mechanistic studies on the oxidation of alcohols by oxo ruthenium complexes will be discussed.

KINETIC AND MECHANISTIC STUDIES OF OXO RUTHENIUM COMPLEXES

Ruthenium Tetroxide

The first kinetic studies for the oxidation of 2-propanol with ruthenium tetroxide in aqueous perchloric acid solutions were investigated by Lee and co-workers.[9] Experimental results showed that two different mechanisms involved at different pH levels. In moderately acidic solutions (1-6.5 M $HClO_4$), the mechanism of the reaction involved a rate-determining hydride transfer, while at high concentrations of acid (7.5-10 M $HClO_4$) carbonium ion formation became the rate-determining step.

Polypyridyl Ruthenium(IV) Oxo Complexes

Preliminary work showed that the ruthenium(IV) oxo complexes $[(bpy)_2(py)Ru(O)]^{2+}$ **(1)** and $[(trpy)(bpy)Ru(O)]^{2+}$ **(2)** (bpy=2,2'-bipyridine, py=pyridine, trpy=2,2',2"-terpyridine) are stoichiometric and/or electrocatalytic oxidants for a variety of alcohols.[10] The reactions were run under mild conditions and were complete within a few minutes.

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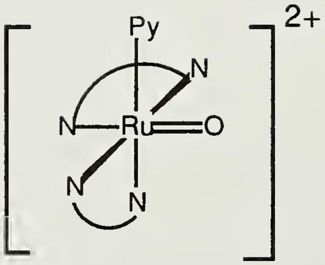
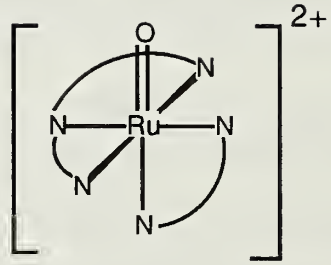


(1)



(2)

The kinetics of oxidation of the alcohols by $[Ru^{IV}=O]^{2+}$ were found to be second order, first order in both alcohol and oxidant. Thus, the rate law under pseudo-first order conditions can be described by the following expression:

$$-d[Ru^{IV}(O)]^{2+}/dt = K[ROH][Ru^{IV}(O)]^{2+} = K_{obs}[Ru^{IV}(O)]^{2+}$$

The reaction between $[(bpy)_2(py)Ru(^{18}O)]^{2+}$ and 2-propanol was studied. The extent of ^{18}O transfer was determined by IR spectroscopy and G.C.-M.S. The labeling experiments showed that the ^{18}O atom in $[Ru^{IV}(^{18}O)]^{2+}$ does not appear in the acetone product. These results indicate a possible hydrogen atom or hydride transfer mechanism. Large α-C-H deuterium isotope effects for methanol $k_H/k_D=9$; 2-propanol $k_H/k_D=5.2$; benzhydrol $k_H/k_D=24$; were observed, which indicates that the reaction involves α-C-H bond breaking in the rate determining step. The large kinetic isotope effect clearly points to a C-H bond breaking in the rate-determining step step. Based on this, two reasonable mechanisms can be proposed. One is a two-electron, hydride transfer from the α-C-H bond of the alcohol to the oxo group of ruthenium(IV), followed by a fast proton transfer, mechanism A (Scheme I). The second plausible mechanism is a one electron, hydrogen atom transfer, followed by a rapid outer-sphere electron transfer and a proton transfer, mechanism B (Scheme II).

Scheme I

$$[\,Ru^{IV}{=}O\,]^{2+} \quad + \quad R_2CHOH \xrightarrow{K} [\,Ru^{II}(OH)\,]^{+} \quad + \quad R_2C^{+}OH$$

$$[\,Ru^{II}(OH)\,]^{+} \quad + \quad R_2C^{+}OH \xrightarrow{fast} [\,Ru^{II}(OH_2)\,]^{2+} \quad + \quad R_2C{=}O$$

Scheme II

$$[\mathrm{Ru^{IV}{=}O}]^{2+} + \mathrm{R_2CHOH} \xrightarrow{K} [\mathrm{Ru^{III}(OH)}]^{2+} + \mathrm{R_2C^{\cdot}OH}$$

$$[\mathrm{Ru^{III}(OH)}]^{2+} + \mathrm{R_2C^{\cdot}OH} \xrightarrow{\text{fast}} [\mathrm{Ru^{II}(OH_2)}]^{2+} + \mathrm{R_2C{=}O}$$

However, a hydrogen atom transfer (radical pathway) appears less likely on the basis of the experimental evidence. First, the presence of oxygen has no effect on the observed rate constant. Second, oxidation of cyclobutanol by $[\mathrm{Ru^{IV}{=}O}]^{2+}$ gives cyclobutanone as the major product, whereas one-electron oxidants give rise to ring-opened products.[11] Finally, the two mechanisms can be distinguished by observing whether $\mathrm{Ru^{II}}$ or $\mathrm{Ru^{III}}$ is formed in the initial step. Experimental results obtained by stopped-flow monitoring of the oxidation of 2-propen-1-ol reveal that the rate of disappearance of $[\mathrm{Ru^{IV}{=}O}]^{2+}$ is equal to the rate of $[\mathrm{Ru^{II}(OH_2)}]^{2+}$ appearance. Clearly, $\mathrm{Ru^{II}}$ must be the initial product, which supports a two-electron, hydride transfer mechanism.

From the combination of rate law, kinetic isotope effect, activation parameters, and product studies, it is clear that oxidation of alcohols by $[\mathrm{Ru^{IV}{=}O}]^{2+}$ complexes occur through an initial preassociation (step 1), followed by a two-electron, hydride transfer mechanism as shown in Scheme III.

Scheme III

$$[\mathrm{Ru^{IV}{=}O}]^{2+} + \mathrm{HC(OH)R_1R_2} \xrightleftharpoons{K_a} [\mathrm{Ru^{IV}{=}O}]^{2+}\mathrm{,HC(OH)R_1R_2} \qquad (1)$$

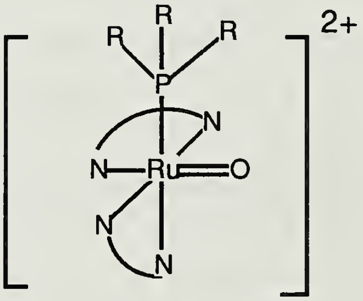
$$[\mathrm{Ru^{IV}{=}O}]^{2+}\mathrm{,HC(OH)R_1R_2} \xrightarrow{K} [\mathrm{Ru{-}O{-}{-}{-}H{-}{-}{-}C(OH)R_1R_2}]^{2+} \qquad (2)$$

$$\longrightarrow [\mathrm{Ru^{II}{-}OH}]^{+} + \mathrm{R_1R_2C^{+}OH}$$

$$[\mathrm{Ru^{II}{-}OH}]^{+} + \mathrm{R_1R_2C^{+}OH} \xrightarrow{\text{fast}} [\mathrm{Ru^{II}{-}OH_2}]^{2+} + \mathrm{R_1R_2C{=}O} \qquad (3)$$

Oxo(Phosphine) Ruthenium(IV) Complexes

Kinetic studies for the oxidation of alcohols by tertiary phosphine ruthenium(IV) oxo complexes $[(bpy)(PR_3)Ru(O)]^{2+}$ **(3)** $\{PR_3 = PEt_3, PPh_3, P(i\text{-}Pr)_3\}$ have been reported.[12] Kinetic data are similar to those observed from polypyridyl oxo ruthenium complexes. In contrast to the polypyridyl ruthenium oxo complexes, the comproportionation rate is very slow between Ru^{IV} and Ru^{II} to give Ru^{III}. Thus, two mechanisms between a hydrogen atom transfer and a hydride transfer can be distinguished by observing UV-Vis spectra changes. From the electronic spectra, it is seen that Ru^{II} is both initial and the final product. No intermediates such as Ru^{III} were observed. These results suggest that oxidation occurs through a two-electron, hydride transfer pathway.



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FURTHER EVIDENCE FOR THE HYDRIDE TRANSFER

Oxidation of Aromatic Hydrocarbons and Formates

Hydride transfer oxidation pathways have also been observed in the oxidation of aromatic hydrocarbons[13] and formates[14] by $[Ru^{IV}{=}O]^{2+}$ complexes. The results of kinetic studies are similar to those observed in the oxidation of alcohols by polypyridyl ruthenium oxo complexes. Experimental evidence in addition to previously discussed support a two-electron, hydride transfer mechanism for the oxidation of alcohols by $[Ru^{IV}{=}O]^{2+}$.

Other Oxometal Complexes

Kinetic studies for oxidation of a series of aromatic fluoro alcohols by permanganate ion have been investigated.[15] The reactions were found to be second order, first order in both alcohol and permanganate. Large kinetic isotope effects were observed (Ph_2CDOH, $k_H/k_D = 6.6$; $PhCDOHCF_3$, $k_H/k_D = 16$). These results suggest that the reaction occurs by a hydride transfer mechanism.

A hydride transfer, oxidation pathway has also been proposed in the oxidation of alcohols by pyridinium chlorochromate (PCC).[16] The reaction was found to be first order in the alcohol and oxidant. Large kinetic isotope effects and a negative ρ value for Hammett plots suggest that the reaction involves a hydride transfer in the rate determining step.

COMPARATIVE KINETIC DATA FOR THE OXIDATION ALCOHOLS BY OXO REAGENTS

Hydride transfer mechanisms for the oxidation alcohols by other oxometal complexes such as RuO_4, MnO_4^-, $[(bpy)_2PR_3Ru(O)][ClO_4]_2$ or CrO_3ClPyH (PCC) have been proposed. Kinetic data for these reactions are summarized in Table I. From the data in Table I, the reactions involving oxo reagents have substantial k_H/k_D kinetic isotope effects and similar patterns in activation parameters. Clear similarities further support the hydride transfer mechanism in the oxidation of alcohols by ruthenium oxo complexes.

Table I. Summary of Kinetic Data on Oxidation of Alcohols by Oxometal Complexes.

Oxidant	Substrate	$\Delta H^{\neq}$ (kcal/mol)	$\Delta S^{\neq}$ (eu)	k_H/k_D	Reaction order
$[(trpy)(bpy)Ru(O)]^{2+}$	$CH_3CHOHCH_3$	9	-34	5.2	second
$[(bpy)_2(PPh_3)Ru(O)]^{2+}$	$CH_3CHOHCH_3$	11	-33	10	second
MnO_4^-	PhCH(OH)Ph	5.7	-38	6.6	second
RuO_4	$CH_3CHOHCH_3$	14	-20	4.6	second
CrO_3ClPyH (PCC)	EtOH	12	-36	5.7	second

CONCLUSION

Ruthenium complexes are useful reagents in the oxidation of alcohols to corresponding carbonyl compounds. The wealth of experimental evidence suggests that the mechanism of the reaction is a two-electron, hydride transfer from the α-C-H bond of alcohol to the oxo group of ruthenium(IV). Labeling studies have revealed that the reaction occurs by a template mechanism in which the oxo group is not transferred to the substrate (alcohol). This suggests that Ru^{IV} oxo complexes can be used in catalytic oxidations.

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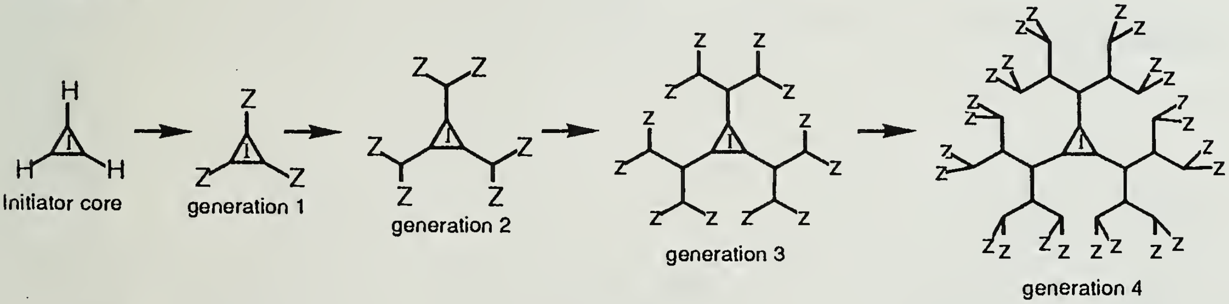
RECENT ADVANCES IN THE SYNTHESIS OF MULTIBRANCHED OLIGOMERS: STARBURST DENDRIMERS, CASCADES, AND ARBOROLS

Reported by Christopher J. Welch November 30, 1989

Introduction

The synthesis of multibranched, radially symmetrical oligomers possessing multiple surface functionality has recently been the focus of intensive investigation.[1] These multibranched oligomers have already proved useful as molecular size calibration standards, demulsifiers, reagents for polymer synthesis, and in drug delivery applications. In addition, use of these molecules as viscosity modifying reagents, molecular hosts for inclusion of guest molecules, ion sequestering reagents, and "platforms" for anchoring catalytic sites have been proposed. Several strategies for synthesis of these oligomers have been reported.[2,3,4,5,6,7] A general synthetic scheme is outlined here in Scheme I. A chain elongation reaction sequence which introduces branching is carried out upon an initiator core. Each succeeding repetition of the process yields a larger, more highly branched oligomer, with increasing numbers of surface functional groups (z).

Scheme I



Cascades

The first report of an iterative synthesis resulting in multibranched oligomers appeared in 1978, by Vögtle and co-workers.[2] Sequential alkylation and reduction steps (Scheme II) permit a multiplication of functional groups in what the authors term a "cascade synthesis". After one iteration, a primary amine gives rise to a product with two terminal primary amines. Another repetition yields a product with four terminal primary amines. Although the authors stopped at the second generation, the process could in theory be repeated,

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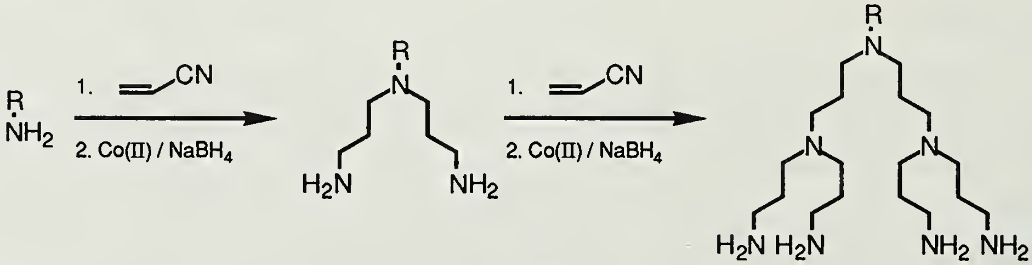
yielding larger oligomers with more terminal amine groups. Diamines were also used to initiate the process, which resulted in dumbell shaped moleules that cascade in two directions. The authors point out that rather than reduction at the nitrile half-generation, hydrolysis to a carboxylic acid terminated oligomer should be possible.

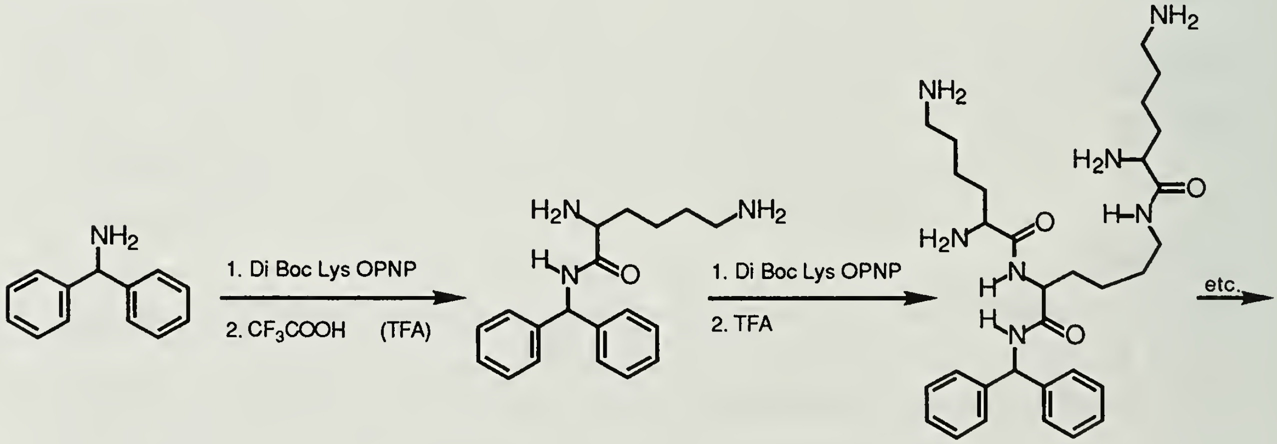
Scheme II



Polylysine

Multibranched polylysine oligomers were described in a 1981 patent granted to the Allied Corporation.[3] In this example (Scheme III) the well known propensity of lysine residues to introduce branching in a growing polypeptide chain has been exploited to form as many as ten generations of multibranched oligomers. A similar patent[8] describes the use of other diamino acids to introduce branching. Investigation of these oligomers[9] has revealed that they are densely packed, with no evidence of the shell-like topology seen in other multibranched oligomers.

Scheme III



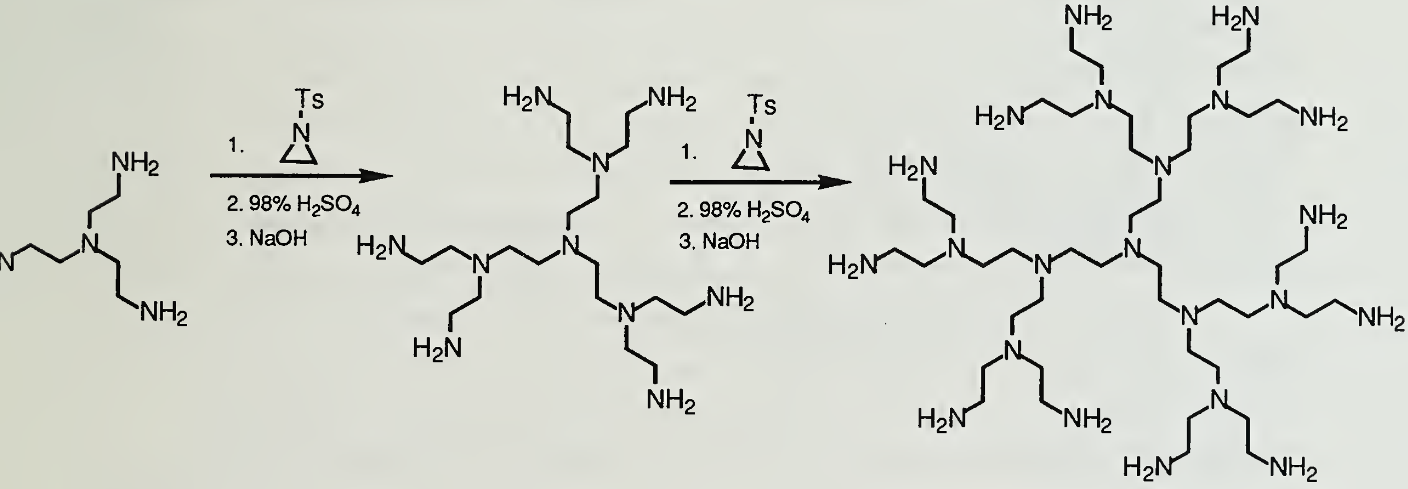
Early Speculations

In 1982, Maciejewski[10] proposed that higher generation multibranched oligomers should be relatively constricted at the surface, while remaining somewhat loose at the interior, possibly allowing for inclusion of guest molecules. In the same paper he points out that the successive addition of new layers to the growing oligomer may become impossible at a certain limiting size due to steric congestion at the oligomer surface. This concept was explored more thoroughly by deGennes in the following year[11], who termed this effect the "starburst limit". He suggested that the starburst limit depends upon the number of reactive sites in the initiator, the length of the repeating unit, and the number of branches introduced in the elongation process.

Dense Star Polyamines

An approach resulting in multibranched polyamine oligomers similar to those shown in Scheme II is described in a 1986 patent[4] issued to Dow Chemical Company. In this sequence (Scheme IV) a triamine is used as the initiator, and chain elongation is accomplished by reaction with N-tosyl aziridine, followed by deprotection. The sequence was carried out to the third generation (not shown) yielding what the authors term a dense star polyamine having 24 terminal amine functionalities. This sequence is expected to give rise to more compact oligomers than the sequence illustrated in Scheme II, due to the more highly branched initiator, and the shorter connecting unit (C_2 vs C_3). The third generation oligomer was shown to form colored precipitates in the presence of copper and uranium ions.

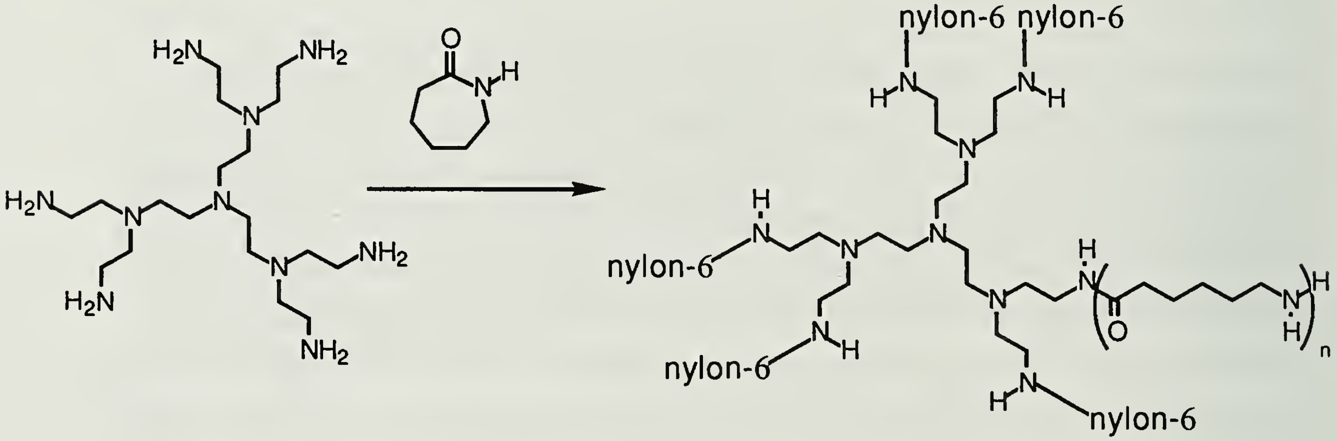
Scheme IV



The second generation dense star polyamine has been reported to form a lamellar liquid crystal in the presence of *n* -octanoic acid.[12] A minimum of about twelve acids per polyamine were determined to be necessary for formation of the liquid crystalline phase, with an interlayer spacing of about 33Å determined by small angle X-ray diffraction.

Synthesis of star-branched Nylon-6 polymers (Scheme V) has been reported using the first generation dense star polyamine as an initiator for the polymerization of caprolactam.[13] Solutions of these polymers were only about 20% as viscous as either linear nylon-6 or a three armed star-branched nylon-6 polymer of of comparable molecular weight. The authors suggest that the star-branched nylon-6 polymers thus obtained may allow lower temperatures or pressures for injection molding.

Scheme V

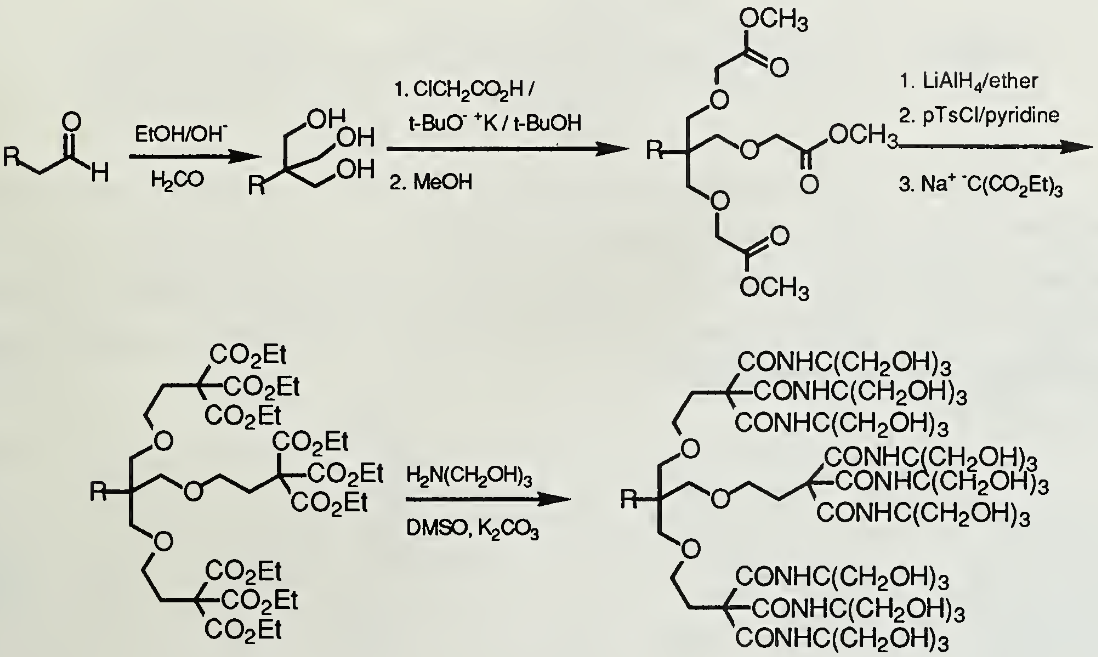


Arborols

Several synthetic approaches[5,7,14] to multiply branched oligomers utilizing alkylations with methane tricarboxylate anion[15], followed by condensation with tris-(hydroxymethyl)aminomethane (Tris) have been reported by Newkome. These molecules have been termed arborols[5], after the Latin word for tree. A stepwise reiterative synthesis with branching occurring at both steps of the elongation process was envisioned, but problems with steric hinderance in the alkylation of neopentyl sites have hampered this approach.[14,16] Nevertheless, fairly large multibranched oligomers have been synthesized.

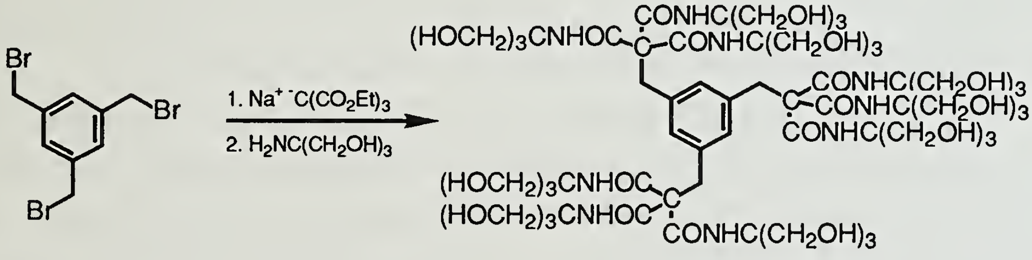
Synthesis of a multibranched arborol[5] is shown below in Scheme VI. An aldehyde was converted to a triol via a formylation / crossed Canizzaro reaction. Chain elongation with chloroacetic acid, followed by esterification and then reduction gave a relatively unhindered extended triol. Tosylation, followed by treatment with methane tricarboxylate anion allowed clean alkylation to give the branched nonaester. Exhaustive transamidation with Tris resulted in a multibranched oligomer containing 27 terminal primary alcohols.

Scheme VI



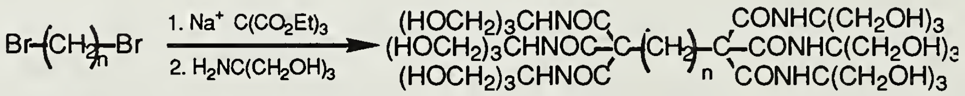
In another approach[7] a trisubstituted benzene moiety was converted into the donut-shaped branched oligomer containing 27 terminal hydroxyls by the procedure outlined in Scheme VII.

Scheme VII

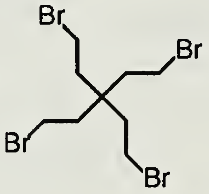


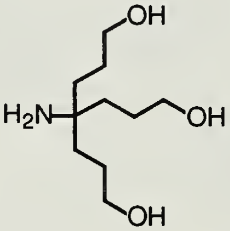
Dumbell shaped molecules[14] were produced when dialkyl halides were used as initiators (Scheme VIII). The compound with n = 10 methylene units was found to form a gel in aqueous solutions. Interestingly, no gelation was observed with the related compounds containing either 9 or 12 methylenes. Examination of the gel by transmission electron microscopy (TEM) revealed long fibers having a uniform diameter of about 36-40Å. A model with cross-packed dumbells was proposed.

Scheme VIII



To date, arborol synthesis using the above described schemes has been severely hampered by problems with nucleophilic displacement at neopentyl centers.[14,16] Newkome has recently reported the synthesis of an initiator core[17] and a branching element[16] which may eliminate this problem, but arborol synthesis using these new compounds has not yet been reported.



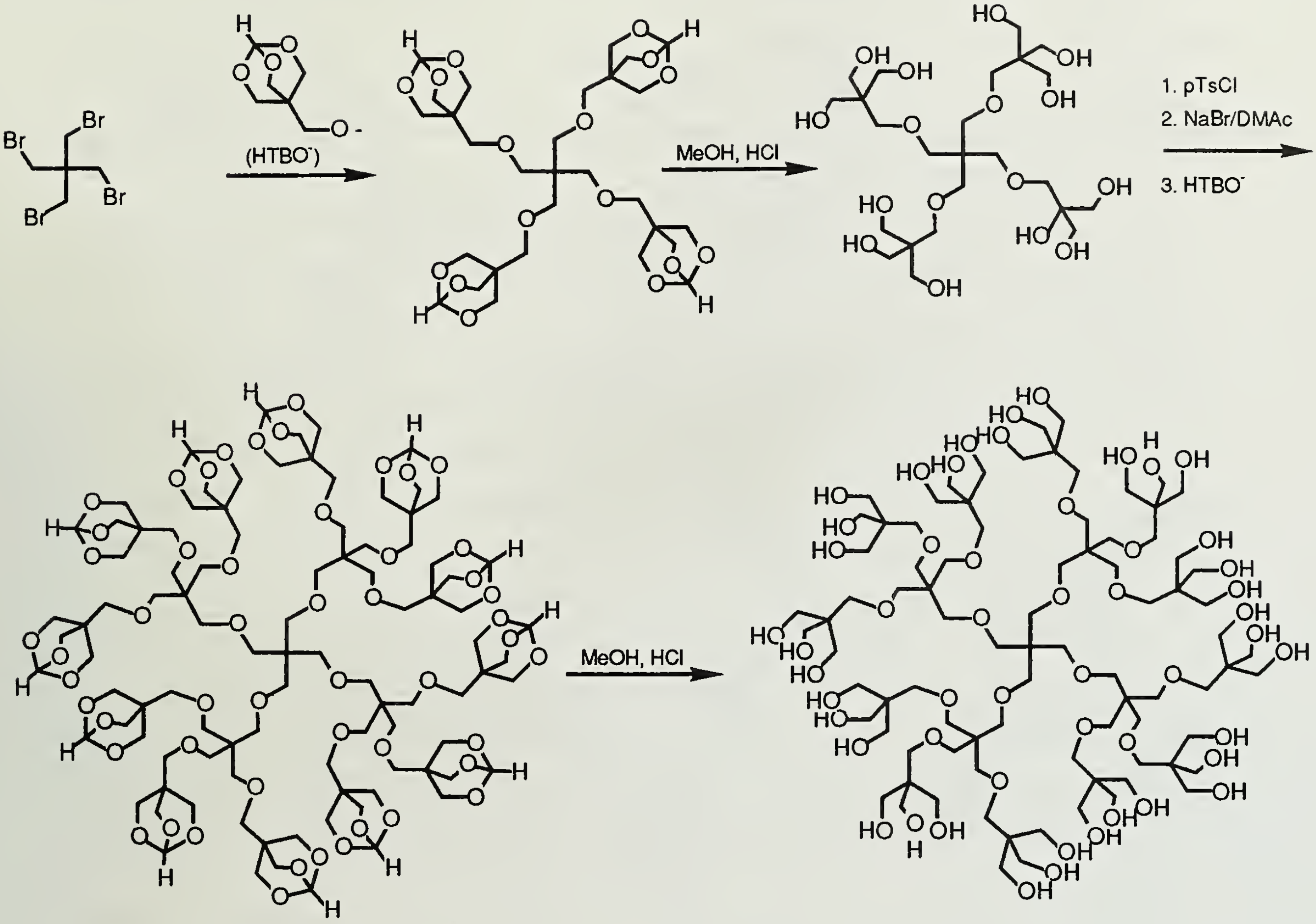


Starburst Polyether Dendrimers

The alkylation problems described above have been largely eliminated in an approach reported by Hall, Tomalia, and co-workers.[6] In this approach, Williamson ether coupling of a synthon containing three primary alcohols "masked" as an orthoformate proceeds smoothly. Successful reiteration of the alkylation/deprotection steps has allowed formation of multibranched oligomers, termed Starburst polyether dendrimers by the authors (after the Greek word for "tree"), up to the third generation (Scheme IX). Similar oligomers with thioether linkages have been reported by the same authors.[18]

Synthesis of the intact fourth generation dendrimer was not possible, presumably because surface density of functional groups prevented complete reaction.[6] Similarly, a molecular model of the fourth generation dendrimer could not be constructed due to congestion. The fourth generation oligomer has been reported to be a forbidden molecular structure, lying beyond the starburst limited generation.[19]

Scheme IX

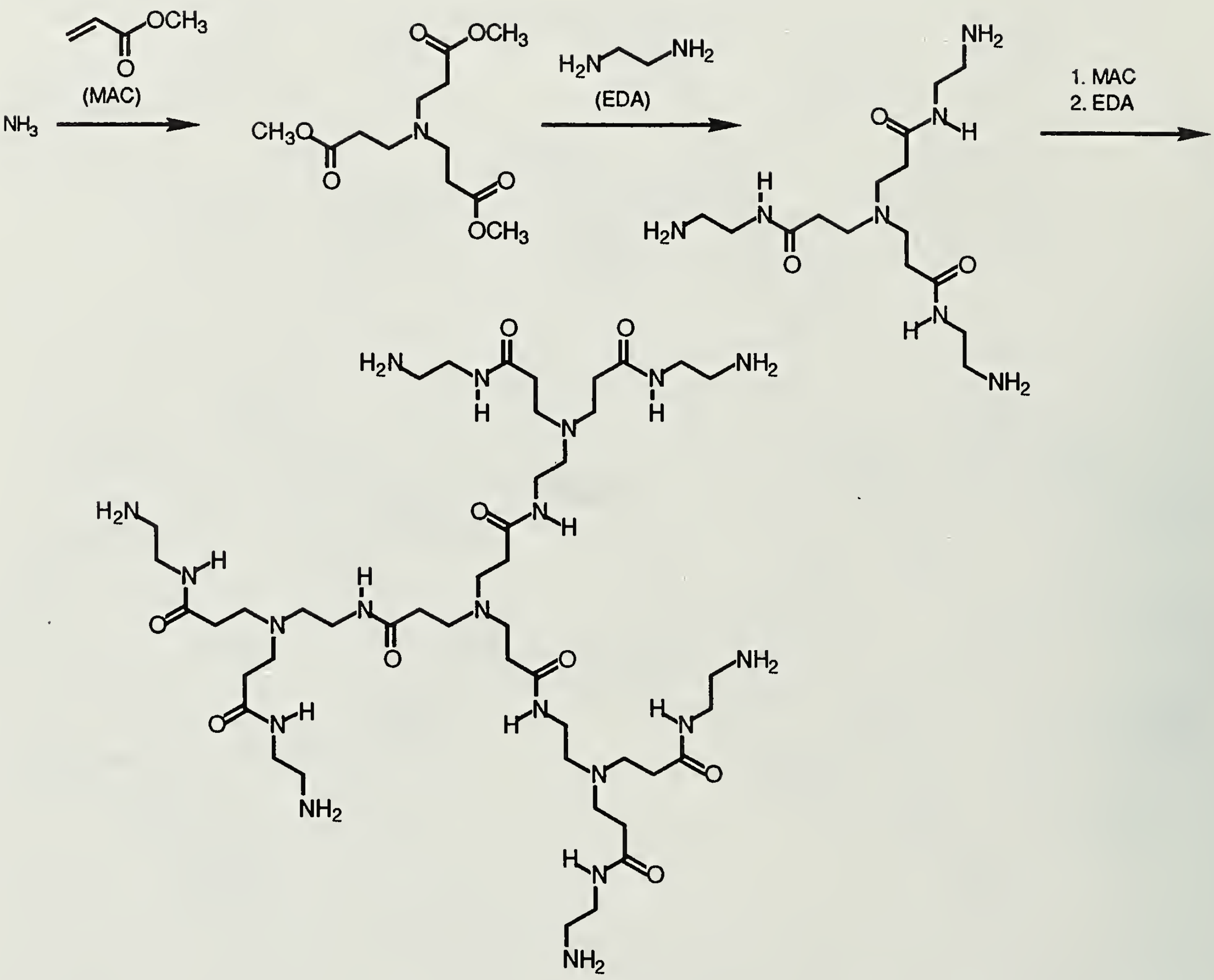


Starburst Polyamidoamines (PAMAMS)

Multibranched polyamidoamines (PAMAMS)[20,21] have been described by Tomalia[22,23] and co-authors. Synthesis of these compounds (Scheme X) is accomplished by a two step elongation/branching procedure consisting of exhaustive alkylation with methyl acrylate, followed by exhaustive transamidation with a diamine such as ethylene diamine.[20] Multibranched oligomers of the tenth generation, which appears to be close to the starburst limit,[19] have been successfully prepared by this procedure.

When ammonia or a primary amine was used as an initiator, spherical dendrimers were obtained at the higher generations, with diamine (e.g. ethylenediamine) initiation resulting in elipsoidal dendrimers.[21] Addition of a large excess of ethylenediamine in the elongation step is necessary to prevent bridging[21] (either intramolecular or intermolecular). Higher temperatures were found to result in bridging defects and to also lead to retro-Michael reactions.[20]

Scheme X



Hydrolysis of ester terminated half generation dendrimers with 1.0 equivalent Group 1 hydroxides (Na+, K+, Cs+, Rb+) resulted in polyanionic spheres which could be directly observed by electron microscopy.[20,21] Measured sizes agreed well with measurements based on examination of CPK models, and with results obtained by size exclusion chromatography and intrinsic viscosity measurements.[20,21]

Measurement of ^{13}C relaxation times by the inversion recovery method have been reported[24] for ethanolamine modified dendrimers. The relaxation time of the terminal carbon was seen to decrease continuously from generation 1-11, reflecting increasing steric congestion at the surface for the higher generation dendrimers.

Rod shaped dendrimers have been obtained[25] by using polyethyleneimine as an initiator for the branching process outlined in Scheme X. Third generation dendritic rods were obtained having diameters of about 25Å and lengths from 1,000 - 5,500Å as determined by TEM.

Applications

The potential use of multibranched oligomers for inclusion chemistry was pointed out very early by Maciejewski.[10] Naylor and co-authors have studied[26] the inclusion of 2,4-dichlorophenoxy-acetic acid and aspirin guest molecules by half-generation carbo-methyoxy-terminated starburst PAMAM dendrimers using ^{13}C spin-lattice relaxation times.

Polymer formation by crosslinking of multibranched oligomers of the PAMAM series has been described.[20,27] For example, heating a mixture of third generation (amino) and 2.5 generation (ester) dendrimers resulted in an amide crosslinked polymer[27].

The use of multibranched oligomers for anchoring catalytic sites has been mentioned.[20] To date, one patent application[28] has described the use a third generation dense star polyamine as a platform for attachment of an antitumor antibody as well as a drug (attached via a labile isothiocyanate linkage). The drug - antibody conjugate was injected into mice, and was observed to be localized in the tumor.

Multibranched oligomers have been suggested as calibration standards for the characterization of sub-micron apertures.[29,20,21] A large variety of these molecules exist in various well-defined sizes, thus they appear to be ideal for calibrating the sizes of micropore filters and membranes, or as standards for SEC or electron microscopy.

CONCLUSION

Multibranched oligomers are a new and interesting class of macromolecules which show great potential for future applications. Although the first member of this class was reported only about ten years ago, some truly spectacular results have already been reported. The potential utility of these molecules for anchoring of catalytic sites, host-guest or inclusion chemistry, or as building blocks for even larger macromolecules is evident, and future applications are anxiously awaited.

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THE MARCUS INVERTED REGION OF THE ELECTRON TRANSFER REACTIONS IN CONDENSED MEDIA

Reported by Yong Zhu December 4, 1989

INTRODUCTION

Marcus theory was originally developed to interpret the rates of outer-sphere electron-transfer (ET) reactions in condensed media.[1] A simple expression of the activation free energy barrier, $\Delta G^{\neq}$, could be derived from the analytical geometry of Marcus' model:

$$\Delta G^{\neq} = (\lambda + \Delta G^{\circ})^2 / 4\lambda$$

where ΔG° is the overall free energy change between reactants and products, and λ is the reorganization energy or "intrinsic" energy as termed by Marcus.[2] In thermoneutral reactions, where $\Delta G^{\circ} = 0$, the barrier is equal to $\lambda/4$, which is called the "intrinsic" activation energy barrier. Marcus theory predicted a bell-shaped correlation of ET rates with reaction exothermicity. The ET rates will initially increase with decreasing ΔG°. When $\Delta G^{\circ} = -\lambda$, reactions become barrierless, and ET rates are maximized. If ΔG° decreases further, ET rates will decrease after reaching the maximum, instead of increase. The region where ET rates decrease with decreasing free energy change (increasing exothermicity) in strongly exothermic reactions is often referred to as the "inverted region".

Marcus theory was proposed more than 30 years ago.[1] Its predictions about the free energy dependence of ET rates for weakly and moderately exothermic reactions have been supported by many experiments, and have been found to extend to many other reactions, such as proton transfer, atom transfer, group transfer, hydride transfer, and S_N2 reactions in the gas phase and in solution.[3] However, Marcus' predictions about the inverted region seemed to have failed in almost all of experiments in solution until the past five years. This abstract will review the recent experimental and theoretical developments in the study of the Marcus inverted region.

BACKGROUND

General Description of ET. According to MO theory, ET between a donor and an acceptor can roughly be described by considering the frontier orbitals of the excited state reactants. An electron jumps from a singly occupied LUMO of the excited donor to the LUMO of the ground acceptor, or from the HOMO of the ground donor to a single occupied HOMO of the excited acceptor. For most intermolecular ET, the distance for orbital interactions between a donor and an acceptor is usually less than 10Å.[4] If the frontier orbitals of a donor can interact with the orbitals

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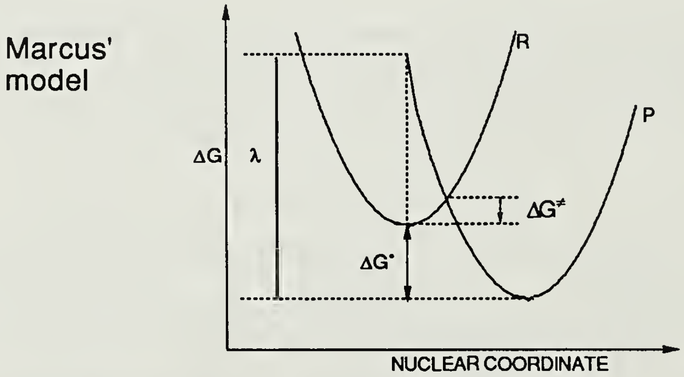
of a rigid spacer or surrounding medium molecules and the interaction of wave functions can propagate to the frontier orbitals of an acceptor, the distance of ET can be more than 10Å, which is called long-distance ET.



Nonadiabatic and Adiabatic ET. In Marcus' model, two parabolas are used to represent the potential energy surfaces of solvated reactants and solvated products (R surface and P surface, respectively). The crossing point of two surfaces represents the transition state of the ET reaction. In an ET reaction, the system has to acquire the activation energy to reach the transition state and change from the R surface to the P surface. One of the most important assumptions in this model is that there is little electronic coupling or orbital interaction between reactants. This is called the zero order state approximation.[1] In this case, the R surface and the P surface will cross each other. The reaction system will pass through the crossing point from the lower R surface to the higher R surface. Theoretically, there is no ET possible without some electronic coupling, since the system has no time to flow along the R surface to the lower P surface. This process is called a "nonadiabatic" process.

In order to achieve an ET reactions, there has to be an electronic interaction between the orbitals of the two reactants. This interaction, leading to a splitting at the crossing point of two zero order states, is called first order perturbation. When the splitting is very large, or when the system moves through the intersection very slow, the system will remain on the lower surfaces from reactants to products. In this case, the probability of ET is unity, and the process is referred to as an "adiabatic" process.

Actual ET reactions usually fall between these two extremes. Reactions with a small probability of ET (near zero) are called nonadiabatic ET or weakly adiabatic ET, and the reactions with a large probability (near unity) are called adiabatic ET. Marcus' outer-sphere ET model is a nonadiabatic model. Marcus assumed that the reaction system would remain on the R surface in the zero order state and move back and forth many times at the crossing point before jumping into the P surface by a first order perturbation. Both reactants and products at the crossing point have the same nuclear configuration.

Reorganization Energy, λ. Marcus' activation free energy barrier contains two contributions: thermodynamic ($\Delta G°$), and kinetic (λ).[3] The nuclear reorganization energy, λ, can be described as the total energy to remove an electron to the P surface from the R surface in a thermoneutral reaction before the nuclear reorganization, while obeying the Franck-Condon principle. This consists of the internal vibrational reorganization energy, λ_i, and the solvent orientational energy, λ_s:[1]

$$\lambda = \lambda_i + \lambda_s$$

In ET reactions, products differ from reactants in bond lengths and bond angles due to gaining or losing an electron. These energy changes are reflected in λ_i. For relatively rigid aromatic molecules, λ_i is usually small because their vibrational structures do not change much in ET processes. The charges of reactants and products are different, so the orientation of solvent molecules surrounding the reactants and products is different due to the dielectric interaction. A more polar solvent leads to a larger λ_s which stabilizes charged products and promotes the charge separation ET reactions, and non-polar solvent usually leads to a negligible λ_s. In Marcus' model the two parabolas represent the two thermal equilibrium zero order states of the system, and the transition state represents the two nonequilibrium states which have the same total energy and equivalent nuclear configurations but a different electron distribution.[4] According to the Franck-Condon principle, the system must be in the transition state geometry before jumping to the P surface from the R surface through the transition state. This means that all the nuclear reorganizations, including internal vibration and solvent orientation, have to occur prior to the actual ET reaction.

Basic Marcus Equations. Actual ET reactions generally involve in the following steps:[5]

$$D^* + A \underset{k_{-dif}}{\overset{k_{dif}}{\rightleftharpoons}} D^* \ldots A \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} D^{+\cdot} + A^{-\cdot} \xrightarrow{k_p} \begin{array}{l}\text{Secondary}\\ \text{processes}\end{array}$$

When applying the steady-state treatment, and assuming that the ET reaction is exothermic: $k_{-a} \ll k_a$, and with consideration of the statistical effects in diffusion step ($k_{dif} \approx k_{-dif}$), a simple kinetic relationship can be derived:[5]

$$1/k = 1/k_a + 1/k_{dif}$$

If ET is much faster than diffusion ($k_{dif} \ll k_a$), the observed ET rate is diffusion controlled: $k = k_{dif}$.
If ET is much slower than diffusion ($ka \ll k_{dif}$), the observed ET rate is activation controlled:

$$k = k_a = A \exp(-\Delta G^{\neq} / RT)$$

In Marcus' model the electrostatic effects of solvents are considered:[4]

$$\Delta G^{\neq} = W^r + (\lambda + \Delta G')^2 / 4\lambda$$

$$\Delta G' = W^p - W^r + \Delta G^\circ$$

where W^r and W^p are work terms involved in bringing the reactants to the encounter distances from infinity, or separating the products to infinity from encounter distances. In highly polar solvents or for neutral molecules the work terms are negligible. If both work terms are equal to zero then Marcus equation can be reduced to:

$$\Delta G^{\neq} = (\lambda + \Delta G^\circ)^2 / 4\lambda$$

The preexponential term A is a function of the probability of collision, electronic state coupling, and the separation distance in the transition state.[5]

Classification of ET Processes. Based on the charge distribution in the reactants and the products, ET processes can be classified as charge separation (CS), charge recombination (CR) and charge shift (CSH) process.[6] CS is defined as occurring when two neutral reactants produce two ionic products by ET. CR is defined as occurring when two ionic reactants produce two neutral products by ET. CSH is defined as occurring when the charge shifts between reactants and products and there is no net charge change in the whole reaction system during ET.

FAILURE OF THE MARCUS THEORY IN THE INVERTED REGION

Weller's Experiment. Marcus' predictions about the dependence of ET rate on the reaction exothermicity have been supported by many experiments in the "normal region", but failed in experiments with very strong exothermicity. One of the famous experiments was done by Rehm and Weller who first studied quantatively the fluorescence quenching of more than 60 typical electron donor-acceptor systems.[7] The most important step in the quenching reaction between excited fluorescing molecules, F^*, and quencher, Q, in polar solvents is ET within the encounter complex $(F^* \ldots Q)$ to produce an ion pair $(F^{(\pm)} \ldots Q^{(\pm)})$. They calculated ΔG° based on the equation:[7]

$$\Delta G^\circ = E_{ox}(D) - E_{red}(A) - E^* + W$$

where $E_{ox}(D)$ is the oxidation potential of the donor, $E_{red}(A)$ is the reduction potential of the acceptor, and E^* is the electronic excitation energy. The electrostatic energy, W, is related to bringing the ions to the encounter distance, r, in the solvent with dielectric constant, ε, and is given by equation :

$$W = q^2 / \varepsilon r$$

They measured the rate constant, k_q, from the relative fluorescence intensity change in quenching reactions with different quencher concentrations, C, based on the equation:[7]

$$I(C) / I(0) = 1 / (1 + k_q \tau_0 C)$$

The experimental results showed that the quenching rate is a function of the total free energy change in polar solvents. For $\Delta G° \leq 5$ kcal/mol, k_q increases sharply with decreasing $\Delta G°$. For thermoneutral ET reaction at $\Delta G° = 0$ kcal/mol, k_q is about 10^9 $M^{-1}s^{-1}$. When $\Delta G° = -10$ kcal/mol, k_q reaches the maximum value which is the diffusion-controlled limit, about 2×10^{10} $M^{-1}s^{-1}$. When $\Delta G°$ decreases further (up to -60 kcal/mol), k_q remains at the diffusion limited rate without decreasing. A bell shaped correlation between k_q and $\Delta G°$, with $k_{q,\,max} = 2 \times 10^{10}$ $M\text{-}1s^{-1}$ at $\Delta G° = -10$ kcal/mol, was calculated based on Marcus equation. The experimental results show a very good agreement with Marcus' prediction in the normal region. However, when $\Delta G° < -15$ kcal/mol, there is disagreement between the experimental and the predicted values. The large deviations for strongly exothermic reactions raised questions about the validities of the basic Marcus theory.

After Weller's experiment, many studies focused on the correlations between ET rate and reaction exothermicity. It was found that ET rates always remain at the diffusion-controlled limit with large exothermicity for most intermolecular ET reaction in polar solvents. No inverted region has been observed for intermolecular CS reactions so far.

Some Interpretations for the Absence of the Inverted Region. Theoretical studies on the interpretation of the absence of the Marcus inverted region have been very popular since Weller's experiment. The main interpretations for the disagreement between experiments and Marcus' predictions are summarized as follows:

A. Weller suggested that the deviations might be partially due to low lying electronic excited states of the ion pair products.[7] When the excitation energy of ion pair is smaller than the reaction exothermicity, the excited ion pair P* surface may intersect with the encounter complex R surface at the minimum area. In this case, the reaction system jumps from the R surface to the P* surface rather than to the P surface. ET will lead to an excited ion pair instead of the ground state product because of the more favorable energy barrier for highly exothermic reactions. ET rates could be much faster than expected, leading to the absence of the inverted region. This process is kinetically more favorable but thermodynamically less favorable. Some recent experiments have supported this proposal.[8,9] Weller noticed,[7] however, that the lowest excited energy of ion pairs in their experiment were all greater than 25 kcal/mol, so this mechanism does not apply to the deviations from -15 to -25 kcal/mol $\Delta G°$ regions. In fact, there is little splitting at the crossing point between the R surface and the P* surface. The interactions between the two states are very weak due to very low electron density and the relatively higher excitation gap of P* state. The excited ion pair states in ET processes have never been observed directly.

B. In contrast to the electronic excitation state, the vibrational excitation state has a much lower energy gap and much higher state density. In large molecules, the vibrational levels with high energies are actually quasi-continuous. Therefore, the system jumping for the ET will always be possible from the R surface to the vibrationally excited ion pair P' surface by thermal fluctuation with a minimum activation barrier.[10] The vibrational interactions between the R and the P' states are essentially similar to the vibrational-electronic interactions between the R and the P* states, but the former interactions are much stronger because they are Franck-Condon allowed. However, the stronger interactions might lead to stronger splitting of the two energy surfaces. The reaction system may become adiabatic. An excited energy transfer pathway would be possible, so Marcus theory may not be applicable in this case.

C. In Weller's experiment,[7] it was found that λ = 10 kcal/mol, which is the same as that calculated by Marcus equation. For strongly exothermic reactions, the separation distances will increase, and then λ will increase(λ> 10 kcal/mol).[10] Based on this assumption, the maximum rate should be higher than the diffusion limit. Therefore, the absence of the Marcus inverted region can be accounted for by the very fast reactions leveled by the diffusion limit. However, for most diffusion-controlled reactions, the levelling effect should be limited based on Marcus' prediction for a bell-shaped correlation. The rate should be lower than the diffusion level somewhere in the highly exothermic region. These rate changes were not observed in Weller's experiment even when $\Delta G° < -60$ kcal/mol. On the other hand, the orbital interactions of reactants will decrease rapidly with increasing separation distances, which leads to little splitting at the crossing point of the energy surfaces. ET would be impossible in this strongly nonadiabatic condition.

D. Close contact between reactants leads to strong orbital interactions between them and consequently a large splitting at the crossing point. An exciplex may be formed in this case.[8] The reaction system will easily pass through the small activation free energy barrier from the R surface to the P surface with high speed. In this adiabatic process the first order perturbation fails,[8] so Marcus equation can not give good predictions for the free energy dependence of the ET rate. The exciplex mechanism may play an important role in the intermolecular ET reactions in solutions, particularly in non-polar solvents, but may not apply for the long-distance ET processes. The ion pairs with long life time have been found in some highly exothermic reactions, implying that these reactions might not be interpreted by the exciplex mechanism.[8]

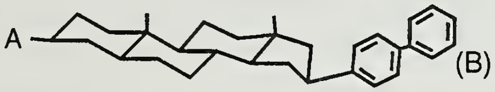
E. For non-adiabatic ET reactions, a quantum tunnelling mechanism seems to be possible.[4] In the normal region, the nuclear tunnelling is very weak because of the wide energy barrier. In the inverted region, however, the energy barrier is much narrower, and the nuclear tunnelling becomes more important. The reaction system can pass through the barrier from the R surface to the P surface without going over the barrier, so the ET rate will be very fast. However, nuclear tunnelling is only one possible pathway. The probability of nuclear tunnelling may not be high enough since the motion of heavy nuclei is quantum forbidden.

All theoretical approaches above are still within the framework of Marcus theory. All the interpretations are limited and far from satisfactory, even though they might be true for some cases. The absence of Marcus inverted region may be interpreted by combinations of these theories.

RECENT EXPERIMENTAL VERIFICATIONS AND SOME THEORETICAL APPROACHES

Miller's Experiment. Miller found in 1979 that long-distance intermolecular ET in rigid matrices conforms to Marcus' prediction for the inverted region. They reported the existence and generality of the inverted region for strongly exothermic ET reactions systematically for the first time.[8] Miller refers to the rate decrease in the inverted region as an "exothermic rate restriction".[8] They examined ET behavior of trapped electrons and 48 organic acceptors in a rigid 2-methyltetrahydrofuran (MTHF) matrix. In the rigid matrix the distances of trapped electrons and acceptors were fixed, which avoids the collisions which seem to lead to the absence of the inverted region in liquid solutions. The highly reducing trapped electrons, which were produced by pulsed radiolysis, generated strongly exothermic ET reactions. Experimental results have shown that the inverted region was apparent and the "exothermic rate restriction" was as large as 10^5 with exothermicity of 45 ~70 kcal/mol, but large deviations existed between the experiment and Marcus' prediction. They proposed that the system jumping for ET from the R surface to the excited product P* surface was the most probable reason for the deviations in the inverted region.[8] When the excitation energies of products were subtracted from their exothermicities, most of data fit the theoretical prediction well. This experiment was the first to support the existence of the electronic excitation ET mechanism. There were still some small amount of data scattered from the theoretically predicted curve after correction with the excitation energy treatment. Miller explained that the small deviations between the experiment and the predictions were probably produced by uncertainties of estimated exothermicities, different reorganization energies and interactions between acceptors and solvents.[8]

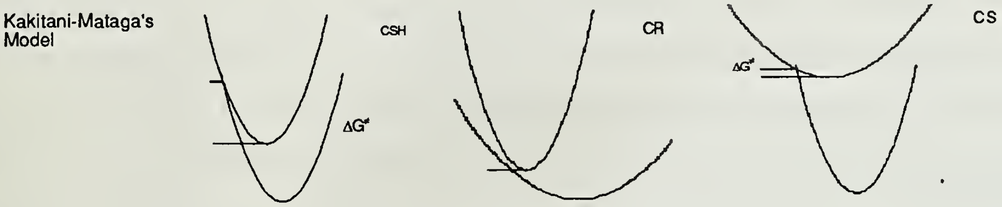
Miller-Closs' Experiment. Miller and Closs extended Miller's work in 1984 by studying the intramolecular long-distance ET in fluid solutions.[9] They synthesized a series of rigid bichromophores with the general structure:[9]



where biphenyl group (B) was an electron donor group, and A were different homologous aromatic electron acceptor groups. Upon subjecting to pulsed solvated electrons, the neutral bichromophoric molecules became radical anions. Electron impact was so fast that the initial electron distribution was far from equilibrium and charge distribution between A and B was almost statistically equal. After capture of an electron, the system would reach equilibrium by ET from B to A through the rigid spacer. The experimental results show a bell-shaped correlation between the ET rate and free energy change in good agreement with Marcus' prediction for the inverted region. This experiment is believed to be the first unambiguous confirmation of the Marcus inverted region for ET reactions in liquid solutions.[9]

According to Marcus theory, when $\Delta G° = -\lambda$, the reaction becomes barrierless and the reaction rate reaches a maximum. When the solvent is changed from polar to less polar for the same reaction system, λ will decrease because the solvation contribution, λs, is smaller in the less polar solvent, and, therefore, maximum rates will occur at the less exothermic region. The experiment confirmed this prediction for the solvent dependence of the ET rate. When ET reactions were conducted in MTHF, $\lambda = 1.2$ eV, and the maximum rate occurred at the more exothermic region. When less polar solvents, either di-*n*-butylether or isooctane, are used, λ is reduced to 0.9 and 0.6 eV, respectively. The bell-shaped curves and the corresponding rate maxima shift to the less exothermic region. This implies that the rates for less exothermic reactions will increase rapidly and the rates for more exothermic reactions will decrease with decreasing solvent polarities.

Kakitani-Mataga's Proposal and Some Arguments. Recently Marcus' prediction for the inverted region has been experimentally confirmed. However, the inverted region in the intermolecular CS reactions has never been observed. The absence of the inverted region in Weller's experiment has not yet been reasonably explained by any theory. More recently, many theoretical approaches have been developed. One of the frontier ET theories is the dielectric saturation effect proposed by Kakitani and Mataga.[6] The charge state of reactants and products will change in ET reactions. The solvent motion around a charged center is more restricted, so the solvent molecules in the solvent first layer may coordinate with the charged center to form a strong solvation shell, where orientation polarization of the solvents is partially saturated. The vibrational frequency of the solvent molecules in the first shell is strongly affected by the charge state of the reactants because of this dielectric saturation effect. The force constant for the solvent vibration around a charged center is much larger than that around a neutral one, which leads to a significantly different potential energy surface in the solvation coordinate. Therefore, the solvation energy surface for charged species is much sharper than that for neutral one, which leads to different activation barriers, particular in the inverted region. This model predicted a different free energy dependence of ET for different processes.[6] For CS process, the ET rate will remain at the diffusion limited rate without decrease at high exothermicity, because the activation barrier between the upper flat surface of neutral reactants and the lower sharp surface of charged products is very small. This leads to fast rates that are independent of free energy change at high exothermicity. For CR process, the ET rate will decrease sharply with increasing exothermicity in the inverted region, because the upper sharp surface of charged reactants may never cross with lower flat surface of neutral products. In this case, the transfer probability of an electron is zero, theoretically. For CSH process, the two surfaces have similar shape, so the ET rate will show medium energy dependence between CS and CR.



Gould and Goodman compared directly the ET behaviors in the inverted region between intermolecular CR and CSH reactions for similar systems.[11] They found that both CR and CSH reactions showed pronounced inverted regions and there was no solvent dielectric saturation effect revealed by their experiment. All of these results contrast to Kakitani-Mataga's predictions. Marcus examined Kakitani-Mataga's model by comparing charge transfer absorption and fluorescence spectra.[12] He could not find any evidence for the existence of dielectric saturation effect either.

Tachiya examined Kakitani-Mataga's model theoretically.[13] He proposed that the solvent polarization in the transition state for CS reactions was far from the dielectric saturation for high exothermicity. The activation barrier should be determined mainly by the R and the P surfaces of the zero order states as predicted by Marcus' model instead of by Kakitani-Mataga's model. He then argued that the absence of the inverted region was not accounted for by the dielectric saturation effect and the basic assumption of Kakitani-Mataga's model was incorrect.

SUMMARY

1. Marcus' prediction for the inverted region has been verified experimentally in intramolecular CR, CSH and CS processes and intermolecular CR and CSH processes recently.
2. The absence of the Marcus inverted region for the intermolecular CS reactions has not been interpreted comprehensively by theories so far.
3. There are several theoretical approaches to interpret the the absence of the inverted region:
a. electronic excitation states involved,
b. vibrational excitation states involved,

c. high reorganization energy involved,

d. formation of exciplexes,

e. nuclear tunnelling,

f. diffusion limitation by collision and / or by solvent relaxation,

g. solvent dielectric saturation effect.

All these theoretical approaches are still in the framework of Marcus theory and all of them have limitations for interpreting experimental results. No direct experimental evidence has been reported for these theories.

4. Further work is needed to solve the problems of the inverted region:

a. new theoretical approaches to be able to interpret all of the experimental results,

b. experimental evidences to test the present theoretical interpretations.

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BARTON'S RADICAL PRECURSOR: APPLICATION IN MECHANISTIC STUDIES AND IN SYNTHESIS

Reported by Jinglin Li December 7, 1989

INTRODUCTION

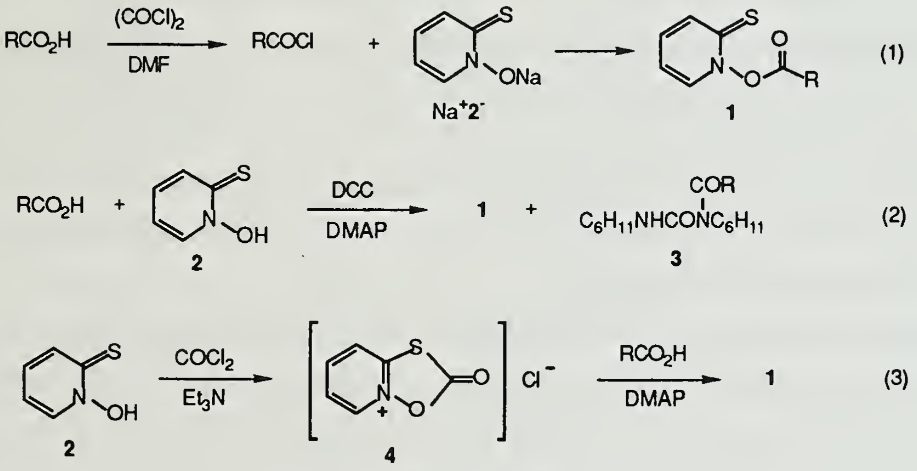
N-Hydroxypyridine-2-thione esters (**1**), first reported in 1983 by Barton and co-workers[1] have been widely used as a convenient and clean free-radical precursor in both mechanistic studies and in synthesis.[2] Among the applications are transformation of functional groups,[2a,3-7] formation of carbon-carbon bonds from addition of a radical to an olefins,[8] kinetic studies such as measuring the rate constants for hydrogen atom transfer to alkyl radicals as well as for the rearrangement of radical-clocks,[9] and the mechanistic investigation of the Gif^{IV} oxidation system.[10] The esters **1** are now often referred as Barton's radical precursor. This abstract will give a brief summary in the studies in which **1** has been used.

BARTON'S RADICAL PRECURSOR

Preparation of *N*-Hydroxypyridine-2-thione Esters (1)

The reaction of a suitably activated carboxylic acid with the sodium salt of *N*-hydroxypyridine-2-thione (Na^+**2**$^-$) results in the formation of bright yellow ester **1**, which can be isolated as a crystalline solid and stored at room temperature with protection from light (Scheme I). Generally, the carboxylic acid is activated by conversion to the corresponding acid chloride (equation 1). Esterification carried out with dicyclohexylcarbodiimide (DCC) and *p*-dimethylaminopyridine (DMAP) is an efficient route for preparation of ester **1** from primary acids, however

Scheme I



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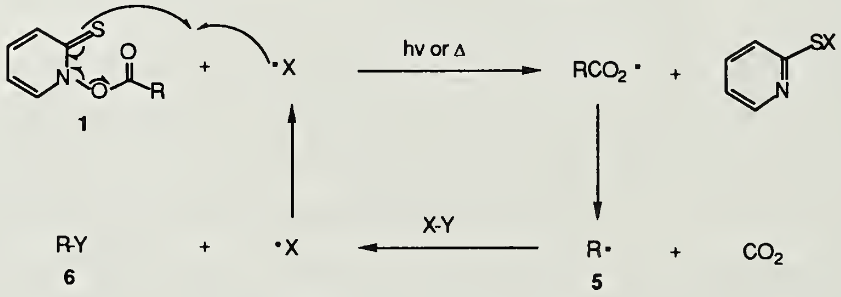
in the cases of secondary or tertiary acids, a major by-product, *N*-acylurea (**3**) is obtained (equation 2). A third method involves the reaction of the carboxylic acid with the cyclic pyridinium salt **4** (equation 3). This method, however, suffers from long esterification times. To date, the most common method to synthesize Barton's radical precursor **1** has been the reaction of derived acid chloride with the sodium salt of **2** as shown in equation 1.

Transformation pathway

The ester **1** will undergo a decarboxylative rearrangement to generate a free radical **5** by either thermal or photochemical initiation. This intermediate radical **5** can be trapped by a variety of neutral molecules (X-Y) to provide the products **6** (R-Y) followed by regeneration of the radical chain carrier (X•), (Scheme II). The general requirements for successful formation of products **6** are that radical **5** must abstract the atom or group X from neutral molecules (X-Y) at a rate more rapid than its direct addition onto the starting ester **1**. Further, the resulting chain carrier (X•) must add to the ester **1** to regenerate the intermediate radical **5** in order to continue the chain propagation.

Scheme II



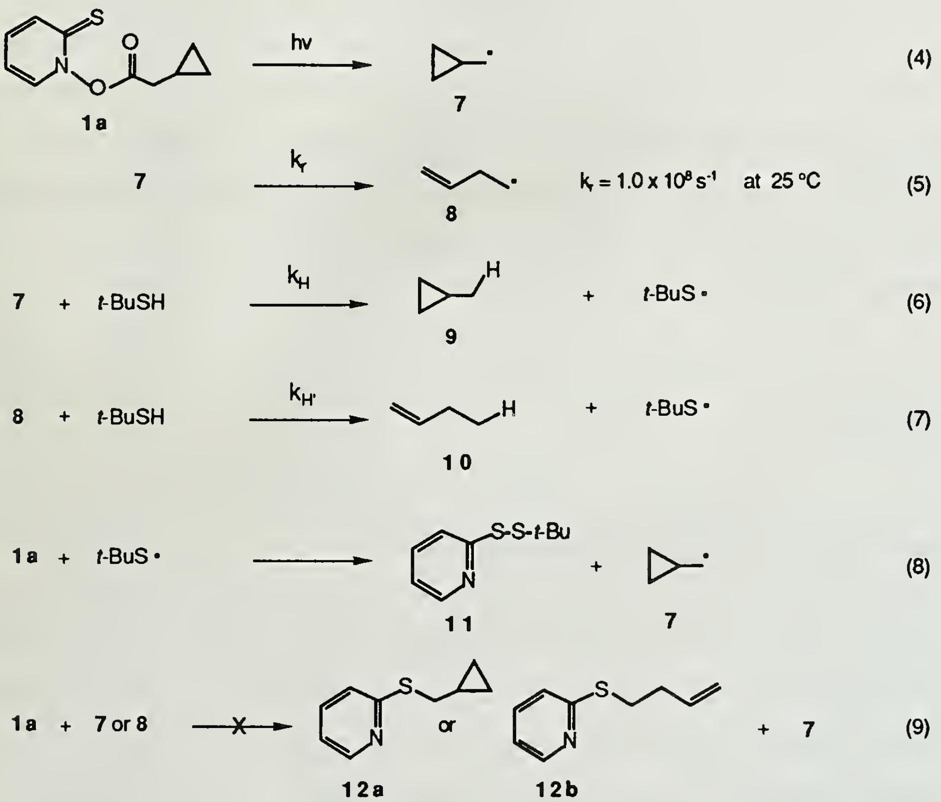
MEASUREMENT OF RATE CONSTANTS FOR RADICAL REACTIONS

The rate constants for reaction of radicals can be measured indirectly by means of competition reactions such as the radical-clock method.[11] In principle, this approach requires that the radical reaction used for comparison has a well-measured rate constant. For practical purposes, a clean source of radicals must be available. Barton's radical precursor *N*-hydroxypyridine-2-thione ester (**1**) promises to provide a convenient source of radicals for kinetic studies. By using the radical-clock method, Newcomb et al. have employed **1** as the free radical precursor to measure the rate constants for several radical reactions such as the reaction of *tert*-butyl thiol (*t*-BuSH) with cyclopropylmethyl radical (**7**) (Scheme III).[9b]

Upon its generation from **1a** with visible light, radical **7** can undergo rearrangement to radical **8** with a known rate constant (k_r) which is used as a "clock" here (equation 5).[9a] In the presence of *tert*-butyl thiol, both radicals **7** and **8** can abstract a hydrogen atom to give the corresponding products **9** and **10** along with the generation of *tert*-butylthiyl radical (*t*-BuS•) (equations 6 and 7).

The *tert*-butylthiyl radical then reacts with precursor **1a** to regenerate the radical **7** along with disulfide **11** (equation 8). Overall the reaction proceeds in a radical chain propagation manner. However, there is a potential competing reaction, in which alkyl radicals **7** or **8** might be trapped by the precursor **1a** (equation 9). According to Newcomb, with *tert*-butyl thiol present in excess, generally there are less than 1% yields of products **12a** and **12b** observed, so this alkyl radical trapping reaction is negligible in the kinetic analysis.

Scheme III

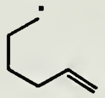


Under pseudo-first order conditions, steady-state treatment gives the rate expression for the reaction of cyclopropylmethyl radical (**7**) with *tert*-butyl thiol as shown in equation 10.

$$k_H = k_r\,[t\text{-BuSH}]^{-1}\,([\mathbf{9}]/[\mathbf{10}]) \qquad (10)$$

Here, k_r is the well-known rate constant for the cyclopropylmethyl radical (**7**) rearrangement [*t*-BuSH] is the average concentration over the course of the reaction and is in large excess. The values of [**9**]/[**10**] are the ratios of the products formed, which can be determined by GC analysis with internal standard. The rate constant (k_H) for the reaction of cyclopropylmethyl radical (**7**) with *tert*-butyl thiol was measured to be 8.0 x 10^6 $M^{-1}s^{-1}$ at 25 °C. Using Barton's radical precursor, radical **7** could be generated over a temperature range from -45 °C to 50 °C. The rate constants (k_H) were obtained at different temperatures, from which could be derived the Arrhenius function, $\log (k_H/M^{-1}\ s^{-1}) = 8.37 - 2000/2.3RT$ for the reaction of radical **7** with *tert*-butyl thiol. By using the same method, Newcomb has been able to obtain the rate constants (k_H) and Arrhenius functions for the reaction of *tert*-butyl thiol with the 5-hexenyl radical (**13**) and 2,2-dimethyl-3-butenyl radical (**14**).[9b]

Newcomb concludes that the use of *N*-hydroxypyridine-2-thione ester (**1**) as a radical precursor can be easily applied in the radical-clock method to measure the rate constants and Arrhenius functions for radical reactions. Additionally, in contrast to the traditional radical sources like alkyl halides which are limited mainly to tin-centered radicals, he also showed that the ester **1** can be used for other kind hydrogen atom donors, such as stannanes (Sn-H), silanes (Si-H) and phosphines (P-H).[9c] Mild conditions for generation of the radical is another advantage of Barton's radical precursor **1**. Furthermore, ester **1** is not subject to potentially undetectable radical chain isomerization which sometimes introduces confusion in alkyl halide probe studies.[12]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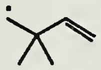
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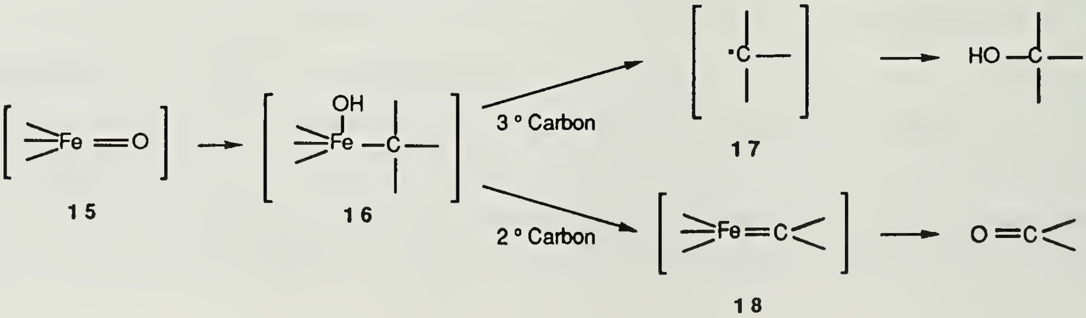
MECHANISM OF GIF^{IV} OXIDATION SYSTEM

Gif^{IV} oxidation system (Zn^0-O_2-Fe^{II}) developed in Barton's group has shown an unusual regioselectivity for oxidation of saturated hydrocarbons.[10,13] In contrast to P_{450} enzyme system, Gif^{IV} oxidation system attacks saturated hydrocarbons in the order of secondary > tertiary. Also, it oxidizes secondary hydrocarbons mainly to ketones, not secondary alcohols. The mechanism proposed by Barton (Scheme IV) is that an iron-oxenoid species **15** is first formed, which inserts to C-H bond to give an intermediate **16**.[10] For tertiary carbons, the iron-carbon bond breaks down to form a tertiary radical **17** and subsequently gives the tertiary alcohol. At the secondary position, the iron-carbon bond is transformed into an iron-carbene complex **18**, which upon cleavage with

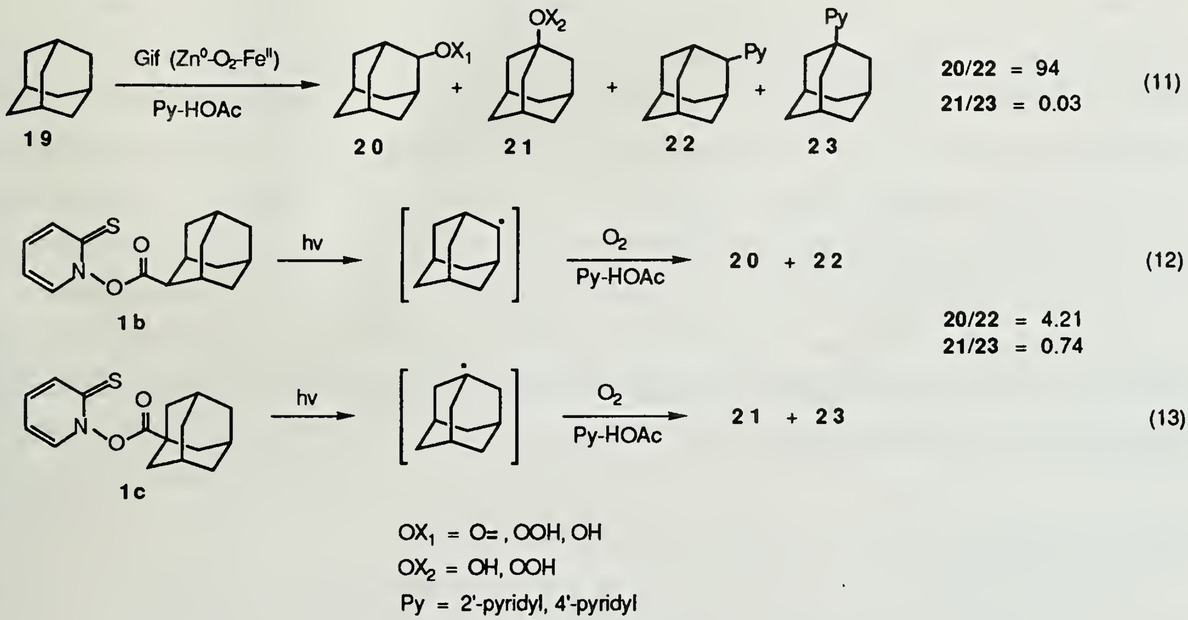
Scheme IV



oxygen or superoxide will give a ketone. Barton suggests that, in the Gif^{IV} oxidation system, the selectivity of oxidation is mainly due to steric bulk of hydrocarbons in which oxygens are attacked.

In the Gif^{IV} oxidation reaction, pyridine and acetic acid are used as the solvent, therefore it is possible to obtain both oxidation products and pyridine coupling products (Scheme V). Clearly high oxygen pressures will favor oxidation products, and lower oxygen pressures will favor pyridine trapping reactions. The development of the radical-generating system based on the ester **1** permits a thorough comparison of oxidation of *secondary* and *tertiary* adamantyl radicals (equations 12 and 13) with that of adamantane (**19**) in the Gif^{IV} system (equation 11).

Scheme V

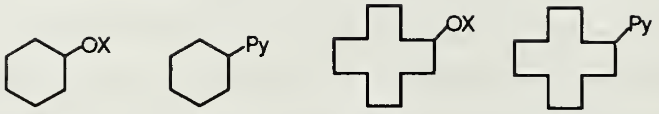


Subsequently two sets of experiments are carried out by Barton.[10] Adamantane (**19**) is first oxidized in Gif^{IV} system, and in a parallel studies, *secondary* and *tertiary* adamantyl radicals are generated separately and then subjected to the Gif^{IV} oxidation system. The same comparisons for cyclohexane and cyclododecane are also carried out under both conditions (Scheme VI). The ratios of oxidation products versus pyridine coupling products are summarized in Table I.[10]

Table I. The Ratios of Oxidation Products vs. Pyridine Coupling Products

	Gif^{IV} oxidation	radical oxidation
20/22 (2°)	94	4.21
21/23 (3°)	0.03	0.74
24/25 (2°)	5.4	0.8
26/27 (2°)	21	3.24

Scheme VI



24 **25** **26** **27**

OX = O=, OOH, OH
Py = 2'-pyridyl, 4'-pyridyl

If free radicals are involved in the Gif$^{\text{IV}}$ oxidation system, these ratios should be similar. Apparently for the secondary position they are not, and Barton proposes that radicals are not involved in the Gif$^{\text{IV}}$ oxidation at the secondary carbon. However, for the tertiary position, a ratio of **21/23** in the Gif$^{\text{IV}}$ system is lower than that of analogous radical experiments. Barton suggests that this arises from pyridine which is coordinated with iron in the intermediate **16** during the Gif$^{\text{IV}}$ oxidation (Scheme IV). When the iron-carbon bond fragments into a radical at the tertiary position, one or more pyridine residues is held close by and probably promotes the pyridine coupling with the resulting tertiary radical **17**. Therefore, more pyridine coupling products **23** will give a lower value of **21/23** in the Gif$^{\text{IV}}$ system than corresponding analogous radical experiments.

From comparison of these results, Barton concludes that radicals are not involved in the Gif$^{\text{IV}}$ oxidation at the secondary carbons. He suggests that the iron-carbene complex **18** is formed in the reaction as shown in Scheme IV.

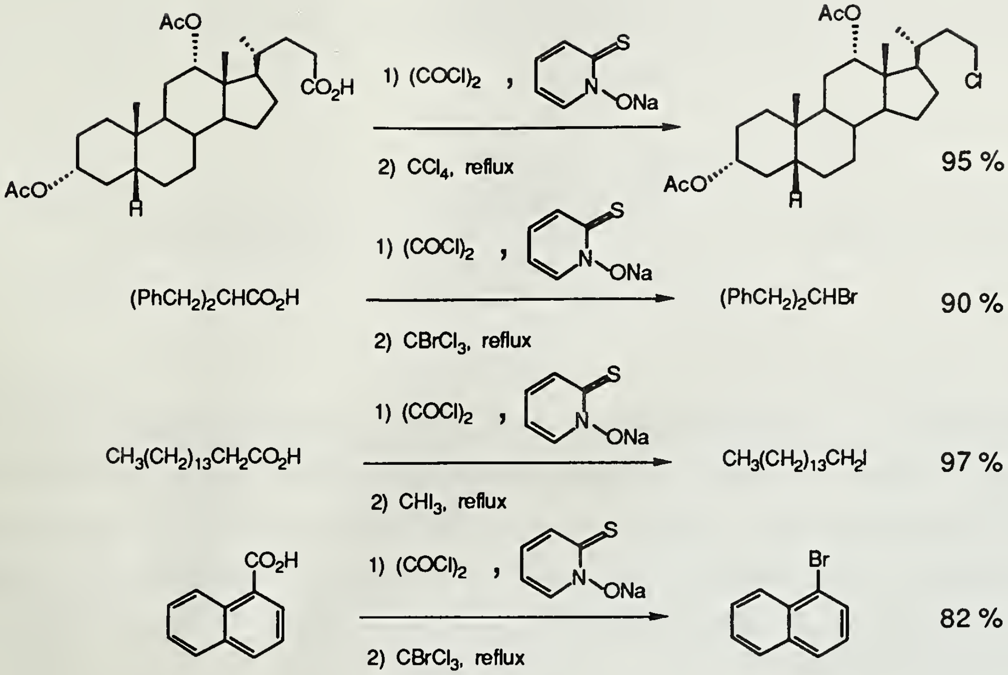
TRANSFORMATION OF FUNCTIONAL GROUPS

It has been shown that a wide variety of functional groups such as halogen,[3] hydrogen,[4] hydroxyl,[5] arylthio[6] and arylseleno[7] can be introduced via radical reactions by using Barton's ester **1**. Generally these functional group transformations proceed with a net decarboxylation.

Halodecarboxylation (The Hunsdiecker Reaction)

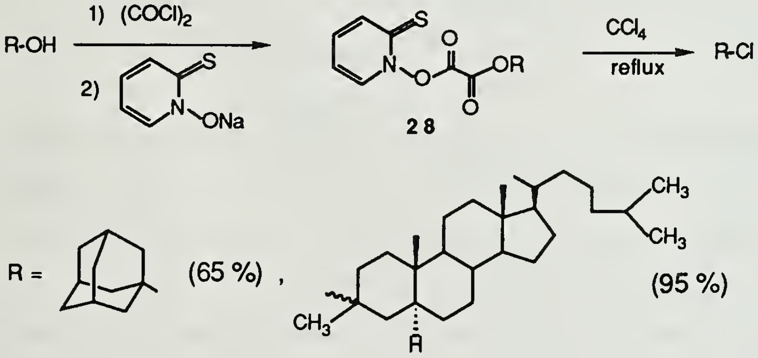
The Hunsdiecker decarboxylation reaction was first reported in 1939.[14] During the past sixty years, several modifications have been described.[15] However, heavy metal salts such as silver, mercury, thallium, copper, and lead are often used. A rather mild reaction for the transformation of a carboxylic acid into its corresponding halide has been developed by using esters **1**. By simple addition of the derived acid chloride to a refluxing suspension of sodium salt of **2** in the solution of carbon tetrachloride, bromotrichloromethane or cyclohexene which contains iodoform will give the corresponding alkyl chlorides, bromides or iodides in ca. 70-98% yields (Scheme VII).[3a] Arylbromides can also be prepared by such method with ca. 43-85% yields.[3c] This is particularly useful since under the normal condition of the Hunsdiecker reaction, arylcarboxylic acid quite often suffers extensive side reactions such as electrophilic aromatic bromination.

Scheme VII



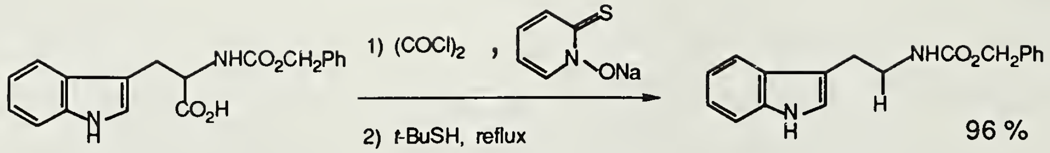
In addition, Crich et al.[3d] reported a facile three-step synthesis of *tert*-alkyl chlorides from the corresponding tertiary alcohols. This reaction was conveniently monitored by the loss of the bright yellow color of the oxalate derivative **28** (Scheme VIII).

Scheme VIII



Reductive Decarboxylation

When ester **1** was heated at reflux in the benzene or toluene with the presence of hydrogen atom donors like tributyltin hydride or *tert*-butyl thiol, the corresponding reductive decarboxylation product is obtained (equation 14).[4a] This method can also be extended to the deoxygenation of tertiary alcohols (equation 15).[4b]



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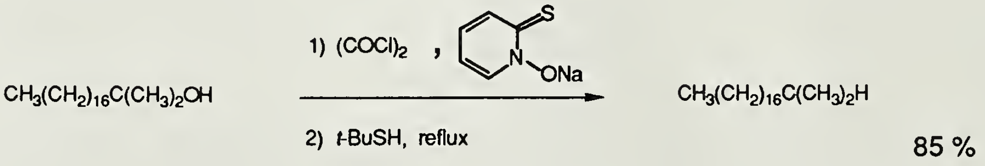
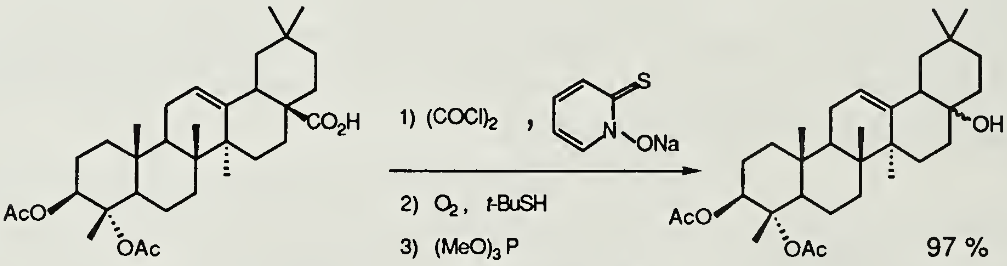


(15)

Oxidative Decarboxylation

Upon generation of radical from Baron's ester, simple passage of oxygen through the solution followed by treatment with dimethyl sulfide or trimethylphosphine gives the corresponding alcohol in ca. 50-97% yields (equation 16).[5] In such transformations, *tert*-butyl thiol was found out to be necessary present in the reaction solution in order to eliminate side reactions. Also in some cases, alkyl hydroperoxide can be isolated as the final product before the addition of dimethyl sulfide or trimethylphosphine (equation 17).[5]



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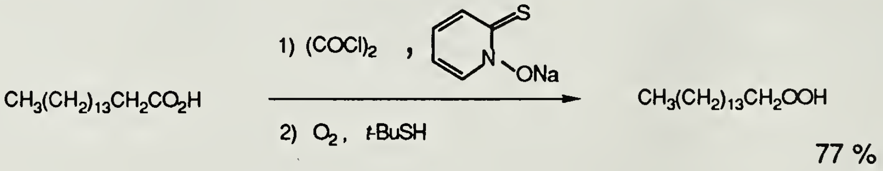
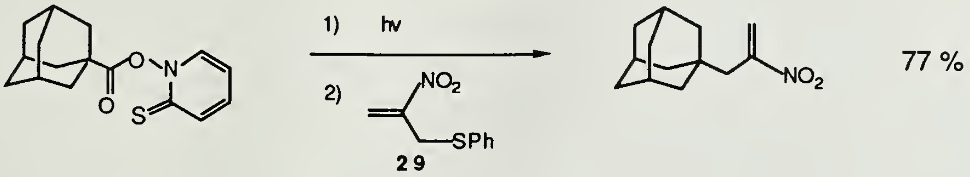


(17)

FORMATION OF CARBON-CARBON BONDS

In recent years, a great deal of effort has been put into the development of radical methods for carbon-carbon bond formation. Typically, that involves the addition of a designed carbon radical to an olefin to give an adduct radical which abstracts hydrogen and generates a radical carrier for subsequent chain reaction. The overall effect is the addition of R· and H· across a double bond.[16] A somewhat different approach to the formation of carbon-carbon bonds by radical methods involves radical addition/elimination reactions. The *tertiary* admantyl radicals can reacts with 2-nitroallyl phenyl sulfide (**29**) with concomitant expulsion of phenylthiyl radical (PhS·) from the allylic position. The resulting phenylthiyl radical then acts as a chain carrier to add onto ester **1** to generate the *tertiary* admantyl radical and keep the chain reaction going. The presence of an electron-withdrawing group on olefin is necessary for efficient addition here (Scheme IX).[8]

Scheme IX



CONCLUSIONS

N-Hydroxypyridine-2-thione esters (**1**), are useful radical precursors which can be activated thermally or photochemically at room temperature or even down to -78 °C. They have proved to be the clean and convenient radical sources for mechanistic studies, and also showed to be superior to the corresponding alkyl halides as radical sources. In addition, they provide an alternative route for decarboxylation and subsequent transformation of functional groups such as halogen, hydrogen, hydroxyl. Especially the halodecarboxylation process appears to offer substantial advantages over the traditional Hunsdiecker reaction.

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Semester II, 1989-90

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SYNTHESIS AND EVALUATION OF A β-AMINO ACID DERIVED CHIRAL STATIONARY PHASE

Reported by John E. McCune January 11, 1990

Since Louis Pasteur first used tweezers to separate crystals of the sodium ammonium salt of tartaric acid into its respective enantiomers, chemists have sought improved methods for the resolution of enantiomeric species. Several factors contribute to the accelerated interest in the development of techniques for enantiomeric purification and methods for monitoring optical isomerism. Most synthetic organic research is directed towards asymmetric synthesis. The organic chemist often requires a method for determining the enantiomeric purity of starting materials or products Enantiomeric purity is becoming an increasingly important issue in the pharmaceutical industry, for enantiomers frequently elicit rather different biological responses. Frequently one enantiomer promotes a desired effect where as the other may be toxic or have little activity. For example, in the well publicized Thalidomide disaster, the drug was marketed as the racemate and one enantiomer was subsequently found to cause serious birth defects.[1] These factors have led the Food and Drug Administration to put increasing pressure on the pharmaceutical industry to develop enantiomerically pure drugs and if the "other" enantiomer is present, even in minor quantities, to determine its toxicity.

In the past decade the use of chiral stationary phases (CSPs) for the direct analytical and preparative separation of enantiomers has enjoyed increasing popularity. The inherent advantages of chromatography; rapid analysis time, the ability to separate complex mixtures, reproducibility, flexibility and economy are extended to the problem of enantiomeric resolution when CSPs are employed.

Considerable progress has been made in the development of synthetic CSPs for the direct chromatographic separation of enantiomers.[2] An inate advantage of synthetic CSPs is the ability to prepare either optical antipode of the CSP as well as the racemic analogs. The preparation and evaluation of CSP **1**, derived from the 3,5-dinitrobenzamide of (*R*)-phenylglycine, for the separation of enantiomers has been reported.[3] We became interested in the effect on enantiomer separations of a second stereogenic center in the CSP as a result of our studies of CSP **1** and other CSPs with a single stereogenic center. To this end, a new β-amino acid derived CSP, **2**, was synthesized and evaluated for the separation of enantiomers.[4] This CSP is conceptually related to the *N*-(3,5-dinitrobenzoyl)-phenylglycine-derived CSP, but has two stereogenic centers and is linked to the silica support through an ester linkage.

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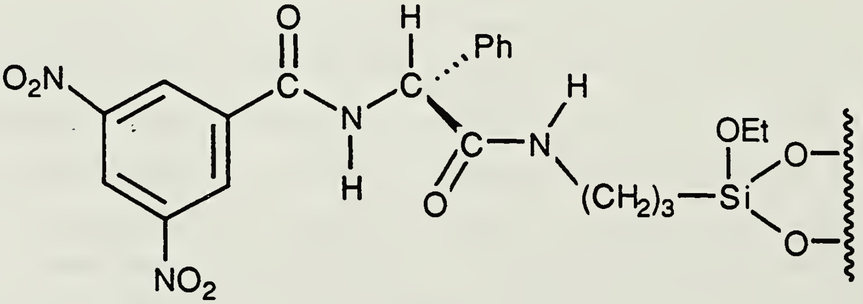
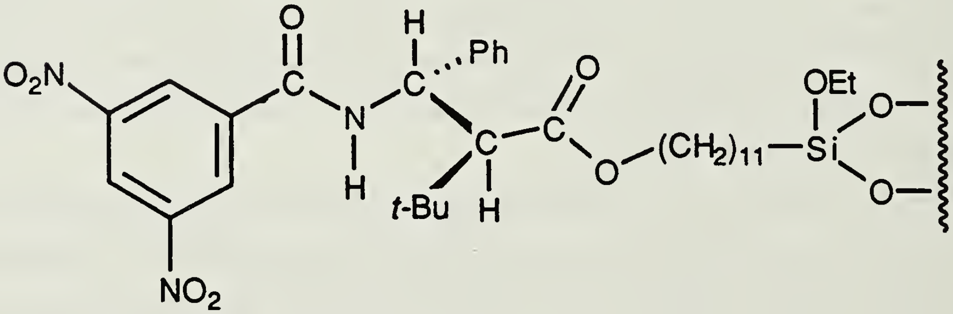
The β-amino acid derived CSP affords superior performance for the separation of many enantiomers, including α-naphthyl carbamate derivatives of chiral alcohols and 3,5-dimethylanilide derivatives of chiral carboxylic acids.[5-7] In contrast to 3,5-dimethylanilides of chiral carboxylic acids, the enantiomers of 3,5-dimethylanilide derivatives of *N*-protected α-amino acids give higher separation factors on CSP **1**.[8]



CSP **1**



CSP **2**

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SYNTHESIS OF SEVEN- AND EIGHT-MEMBERED CYCLIC ETHERS

Reported by Wheeseong Lee February 8, 1990

INTRODUCTION

Medium rings are significantly strained and are not common in natural products. However, seven- and eight-membered cyclic ethers are frequently encountered structural features in naturally occurring substances such as zoapatanol, isolaurepinnacin, isoprelaurefucin, laurencin, laurenyne, and brevetoxin A and B (Fig.1).[1] In view of the increasing number of biologically active natural products containing seven- and eight-membered cyclic ether derivatives, these structural units have become important synthetic targets. However, the construction of seven- and eight-membered rings remains a formidable problem in organic synthesis owing to the severe difficulties caused by transannular interactions, entropic disfavor, angle deformation, and bond opposition forces.[2]

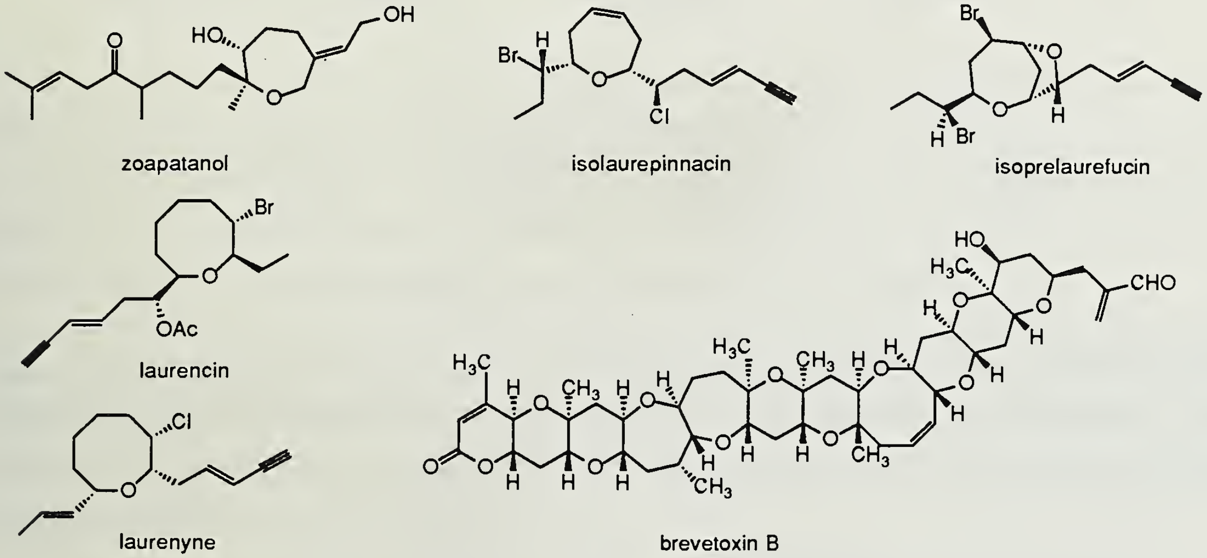
zoapatanol isolaurepinnacin isoprelaurefucin laurencin laurenyne brevetoxin B

Figure 1. Representative seven- and eight-membered cyclic ethers in natural products

STRUCTURE

Medium rings are significantly strained, different conformations having different distributions of strain.[3] By gas-phase electron diffraction , the average length of C-O, C-C, and C-H bonds in oxepane are 1.419Å, 1.531Å, and 1.105Å respectively. There are four possible conformations of oxepane, the 7-membered cyclic ether (Fig. 2), the twist-chair conformation

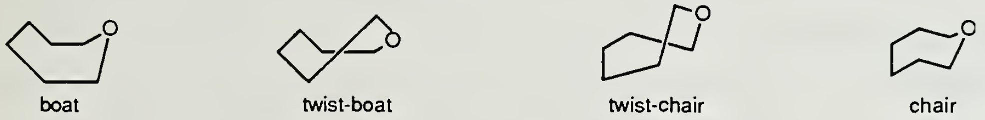
boat twist-boat twist-chair chair

Figure 2. Conformational isomers of oxepane

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which has a lower energy than does the boat, twist-boat, or chair conformations.

In the case of cyclooctane, there are three different families of conformations (Fig. 3). Experimentally, at room temperature, about 5% of the cyclooctane molecules are in crown family conformations (mostly twist-chair-chair) at any instant. The remaining 95% are in the boat-chair family conformation (mostly boat-chair). The boat-boat family is relatively unimportant as the energies of these are calculated to be quite high for cyclooctane (Fig. 3). Similarly, empirical force field calculations on oxocane, the eight membered cyclic ether, reveal that the boat-chair conformation is the most stable structure.[4] In the X-ray structure of the oxocane natural product, laurencienyne,the boat-chair conformation was found (Fig. 4).

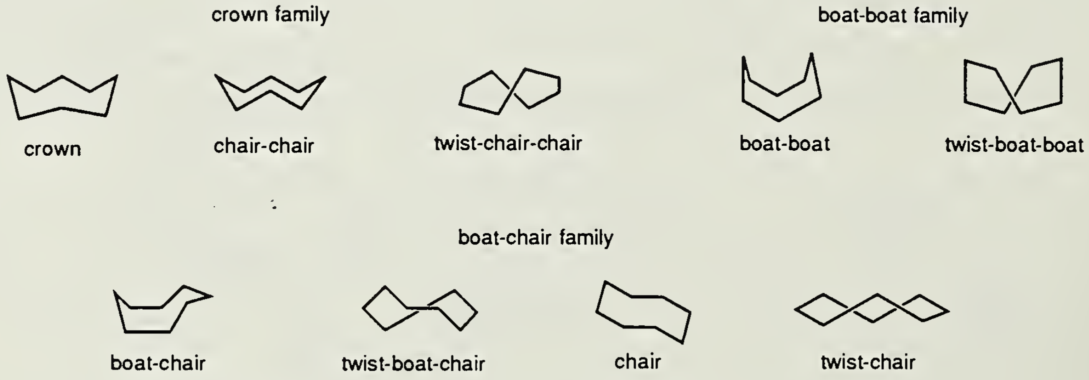


Figure 3. Conformational isomers of cyclooctane

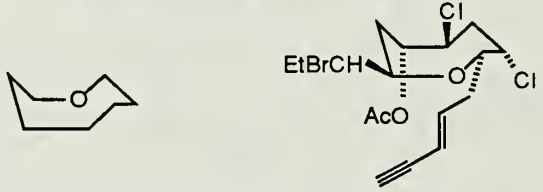


Figure 4. The most stable conformation of oxocanes

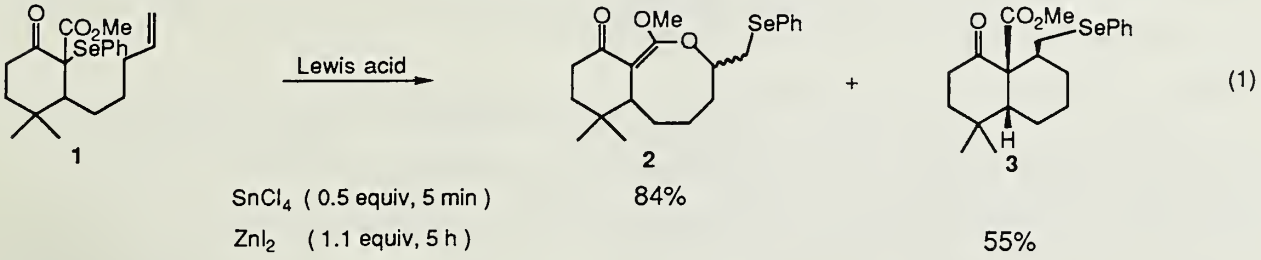
SYNTHESIS OF SEVEN- AND EIGHT-MEMBERED CYCLIC ETHERS

There are three reported approaches to the synthesis of the oxacycles: C-O bond-forming cyclization, C-C bond-forming cyclization, and transformation of the corresponding lactone.

C-O BOND-FORMING CYCLIZATION

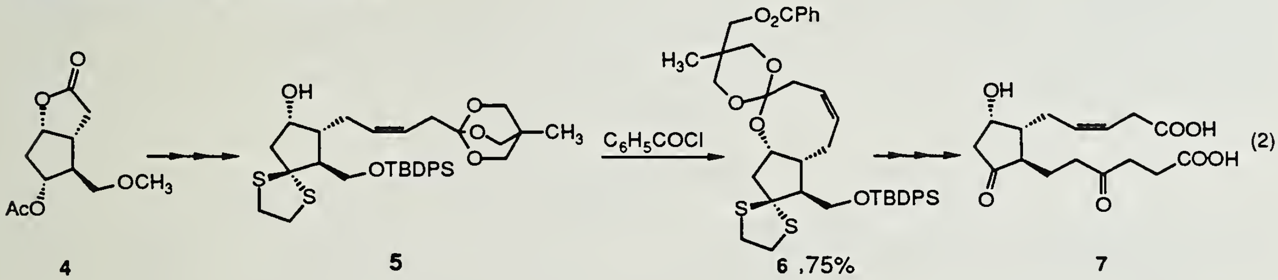
Intramolecular nucleophilic displacement reactions have been widely used in the synthesis of seven- and eight-membered ring ethers. The most common synthesis involves the elimination of water from a diol using strong acid.[6] Cyclization of 7-bromoheptanol under basic condition gives a poorly characterized product in only 5% yield.[7] Reaction of heptane-1,7-diol with hydrogen bromide at 200 °C gives only 1% of an impure product, but treatment of this diol with Naflon-H (a superacidic perfluorinated resin sulfonic acid) at 130 °C gives oxepane in 51% yield.[8] In 1974, Mihailovic allowed 7-octen-1-ol to react with lead tetraacetate and reported the formation of two oxocanes,[9] each in 10-11% yield. The preceding methods are either ineffective or unattractive because of low yields or the vigorous reaction conditions are required.

In 1981, Ley reported a cyclization via a rearrangement of alkenyl-subsituted α–phenylseleno-β-ketoesters, **1**, in the presense of acidic catalysts (eq 1).[10] As seen eq 1, $SnCl_4$

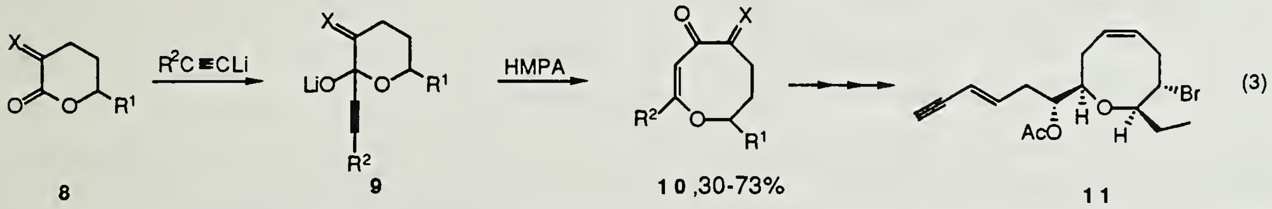


selectively affords cyclization product **2** via the enolic oxygen atom (O-cyclization) and ZnI_2 affords cyclization product **3** via the central carbon atom of the β-ketoester unit. In general, O-cyclization product **2** is obtained if the reaction is worked up after a short period of time (kinetic product) and C-cyclization product **3** is obtained if the reaction is allowed to proceed for a longer period of time (thermodynamic product).

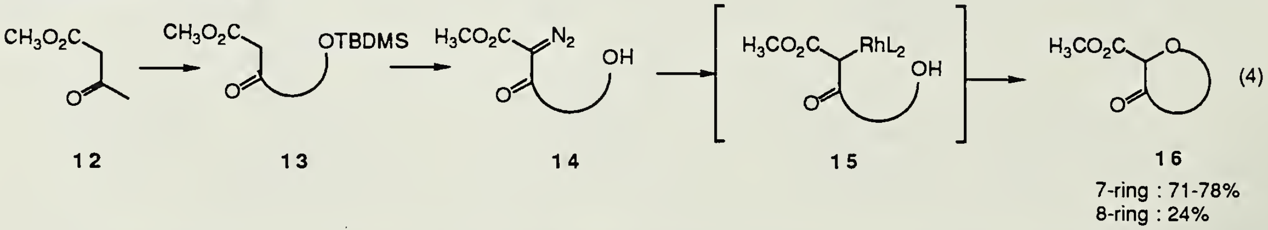
Corey reported the formation of an oxocene-ortho ester derivative **6** from hydroxy ortho ester **5** by the reaction of 3 equivalents of benzoyl chloride and 6 equivalents of pyridine in methylene chloride at 23 °C for 4 h. Internal ortho ester **6** was obtained in 75% yield (eq 2).[11] Clearly, pyridinium chloride is sufficiently acidic to catalyze isomerization of **5** to an eight-membered cyclic ortho ester **6**.



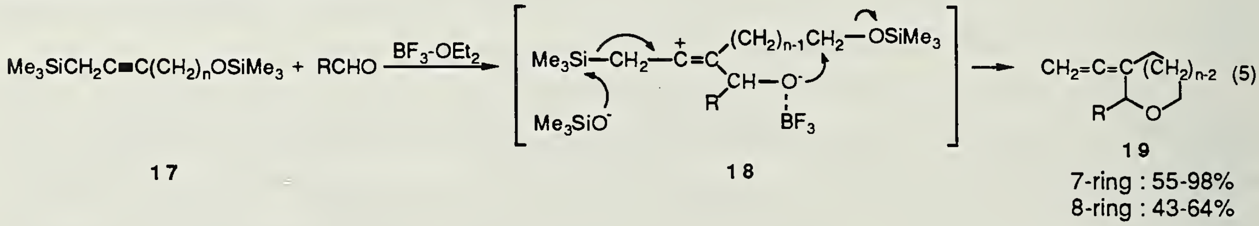
In 1984, Schreiber reported the ring expansion of δ-lactones, **8**, to oxocenes, **11**, by insertion of an acetylide anion followed by Michael-type transformation (eq 3).[12] The ring expansion is presumed to occur by ring opening of the hemiketal addition product, **9**, followed by an intramolecular endocyclic conjugate addition to the resultant acetylenic ketone.



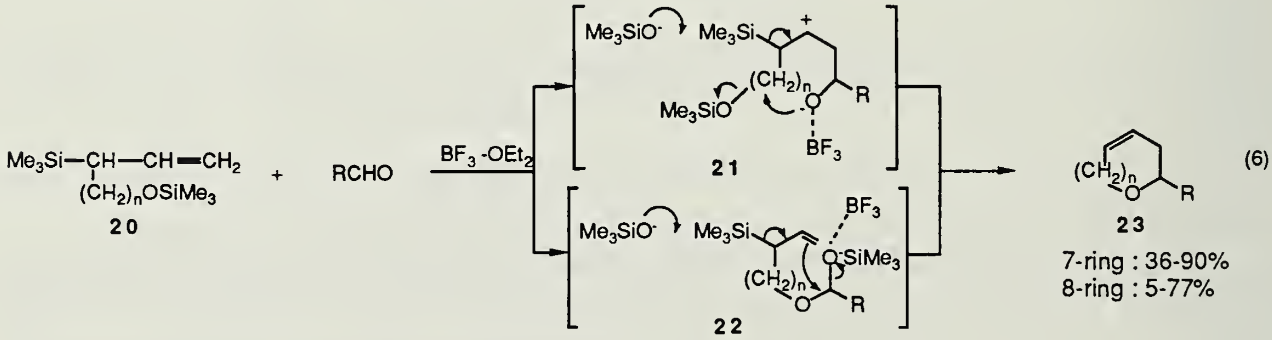
Moody prepared cyclic ethers by rhodium carbenoid cyclization.[13] That is, the rhodium(II) catalyzed decomposition of diazocarbonyl compound **14** involves a metallo-carbenoid intermediate which retains the highly electrophilic properties associated with free carbenes. Therefore, in an appropriate acyclic substrate, such an intermediate would be intercepted intramolecularly by a nucleophile to effect overall cyclization (eq 4). The rhodium carbenoid cyclization to 7-membered ring ethers occurs easily in good yield. The formation of the 8-membered ring ether, albeit in low yield, is particularly noteworthy since 8-membered rings are among the most difficult to form by any ring closure method.



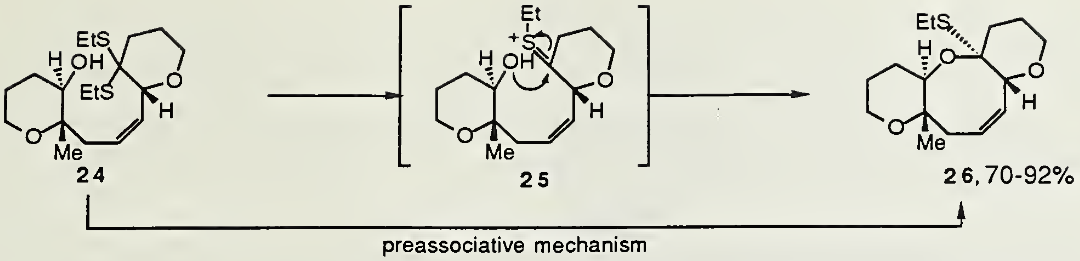
In 1986, Miginiac reported the formation of seven- and eight-membered cyclic ether derivatives from the reaction of ω-silyloxypropargyltrimethylsilanes, **17**, with aldehydes in the presence of BF$_3$·OEt$_2$ (eq 5).[14]



Recently, Miginiac reported the same type of reaction from ω-silyloxyallyltrimethyl-silanes, **20**, and aldehydes (eq 6)[15] to affords oxocenes and oxepenes in a good yield.



In 1986 and 1989, Nicolaou reported an efficient cyclization reaction of hydroxy dithioketals leading to oxocenes as a part of the polycyclic framework of brevetoxin B.[16,17] Nicolaou chose hydroxy dithioketals as cyclization precursors. Because the 8-membered ring is the most strained in the system, he designed a synthetic strategy involving a cationic or a preassociative mechanism in line with the postulate that strain in the transition state would be minimized if kinetic assistance of the nucleophilie is decreased in comparison to a classical S$_N$2 reaction. The looser the transition state, the less effect the strain of the product will have upon activation energy (eq 7).



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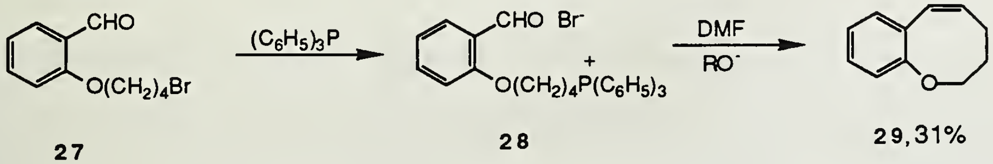
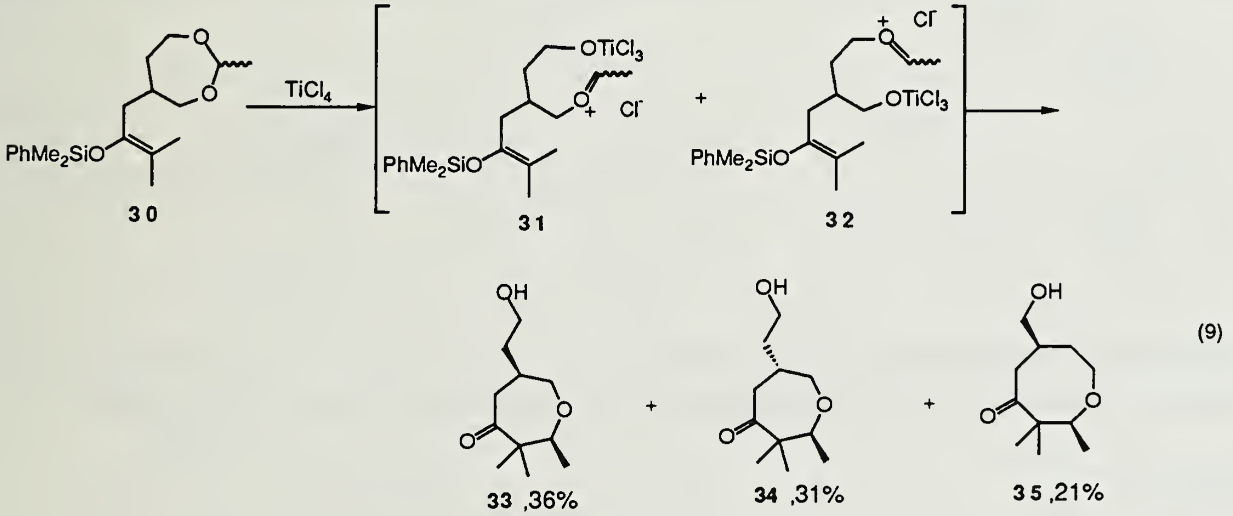
C-C BOND-FORMING CYCLIZATION

In 1974, Schweizer reported the cyclization of an ylide derived from a phosphonium salt to give oxocene in low yield (eq 8).[18] This reaction depends on the nature of solvent, and DMF was selected as optimum.



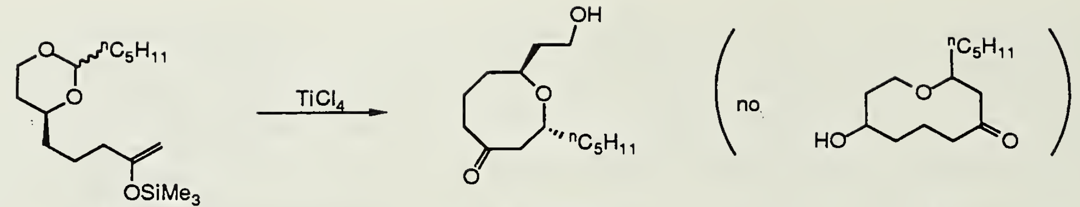
(8)

In 1985, Kocienski reported the preparation of seven- and eight-membered cyclic ethers by using a Lewis acid-catalyzed intramolecular directed-aldol condensation of enol silanes and acetals.[19] The first stage involves Lewis acid-catalyzed cleavage of an acetal to a trigonal oxocarbenium ion and the second stage involves intramolecular capture of the oxonium ion by a trigonal enol silane (eq 9). The inseparable 1:1 mixture of the diastereomers of dioxepane **30** reacts with 2 equivalents of $TiCl_4$ in CH_2Cl_2 at -78 ^oC to give oxepanones **33** and **34** and oxocanone **35** in 88% combined yield. From several examples, a clear preference for cyclization



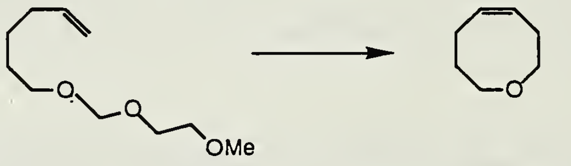
(9)

to the smaller of the two rings was noted. Notably, reaction of **36** with $TiCl_4$ gives only product **37** as a single diastrereomer in 43% yield. No **38** was detected (eq 10).

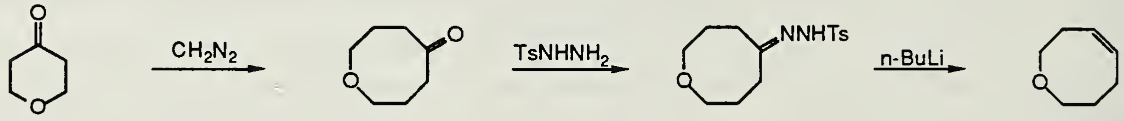


36 **37** ,43% **38** (10)

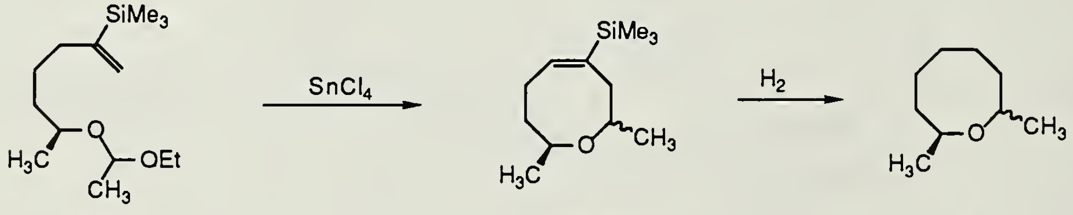
In 1986, Overman demonstrated for the first time that eight-membered cyclic ethers containing Δ^4-unsaturation can be prepared in good yields by direct cyclization of simple unsaturated acetals (eq 11).[20] This method is significant because it is possible to prepare oxocene from commercially available 5-hexen-1-ol in two steps. Comparison of this method with the original low-yield synthesis (eq 12) of this oxacyclic underscores the significant advantage of Overman's direct cyclization method. Treatment of ethoxyethyl acetal **45** with two equivalents of SnCl$_4$ at -20 ^{o}C for 1 h gives a 30:1 mixture of cis- and trans-2,8-dimethyloxocene products **47** (eq 13). A possible explanation for the formation of the unsaturated oxocyclic products is the occurance an intramolecular ene reaction (Scheme 1).[21] This highly stereo- and regioselective cyclization method is useful for the synthesis of unsaturated eight-membered cyclic ethers.



39 **40**,10% (11)

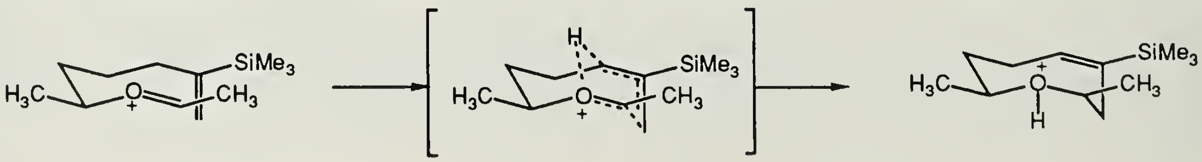


41 **42** **43** **44** (12)



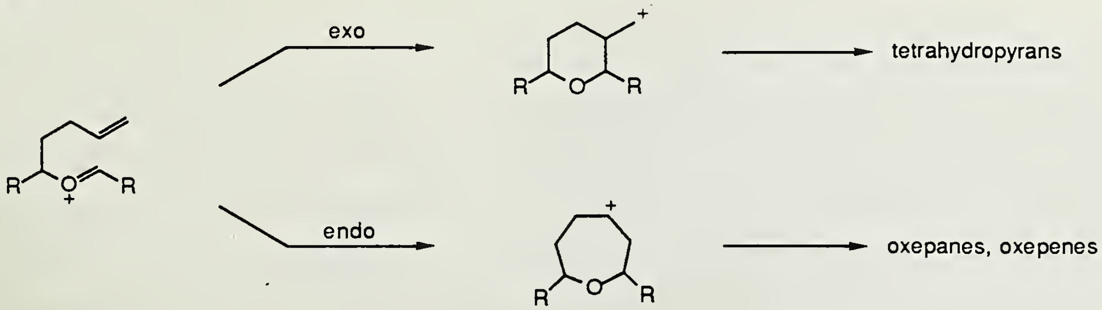
45 **46** ,51% **47** (13)

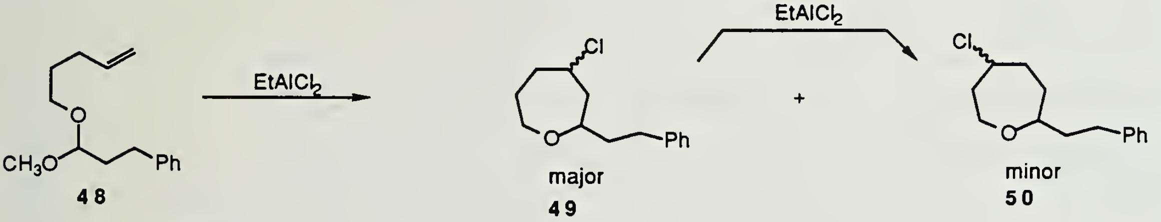
Scheme 1



In 1989, Overman reported the preparation of seven membered cyclic ethers by Lewis acid promoted cyclization of mixed acetals derived from 4-alken-1-ols.[22] The ring size is primarily determined by the electronic bias of the alkene participant. There are two pathways to cyclize 4-alkene-1-ol derivatives (Scheme 2). When a terminal alkene with no C-4 or C-5 substituent, 48, is used, cyclization products are a mixture of cis- and trans-oxepanes 49 and ether regioisomers, 50 (eq 14). However, alkenes with silicon substitution at C-4, such as 51, and 52 cyclize preferentially in the endocyclic mode to give Δ^4-oxepene product 53 in very high yield (eq 15) consistant with the observation that primary β-silyl carbocations are less stable than α-silyl tertiary carbocations. Finally, alkenes with silicon substitution at C-5, such as the mixed formaldehyde acetal 55, were converted in good yield to 3-oxepene, such as 56. However, the closed related mixed aldehyde acetal, 58, does not afford a significant amount of an oxepane product (eq 16).

Scheme 2





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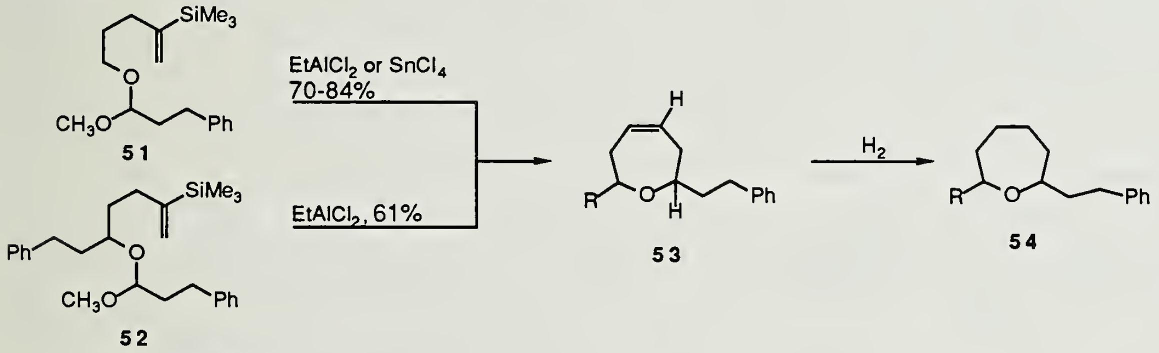

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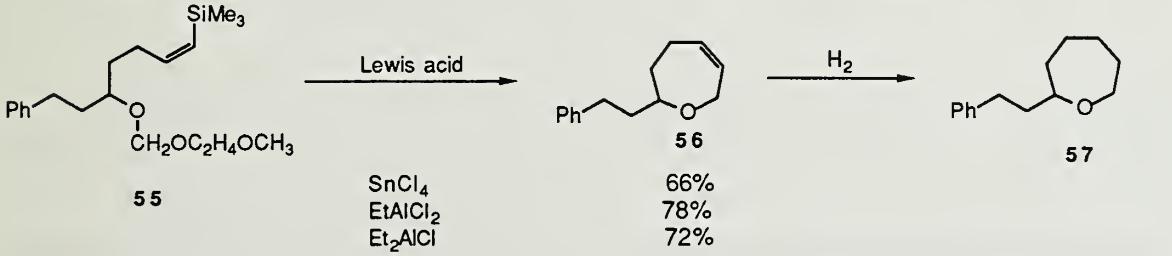

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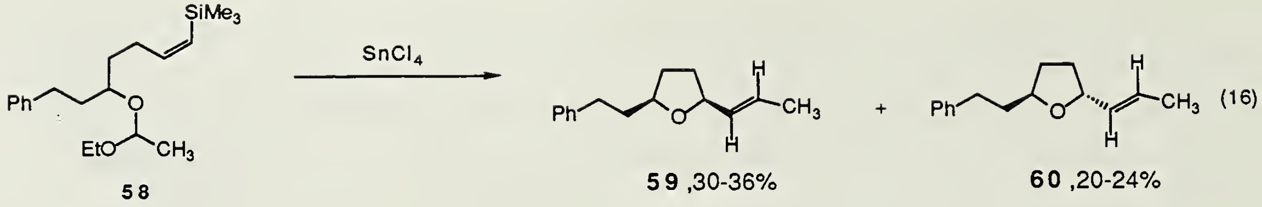
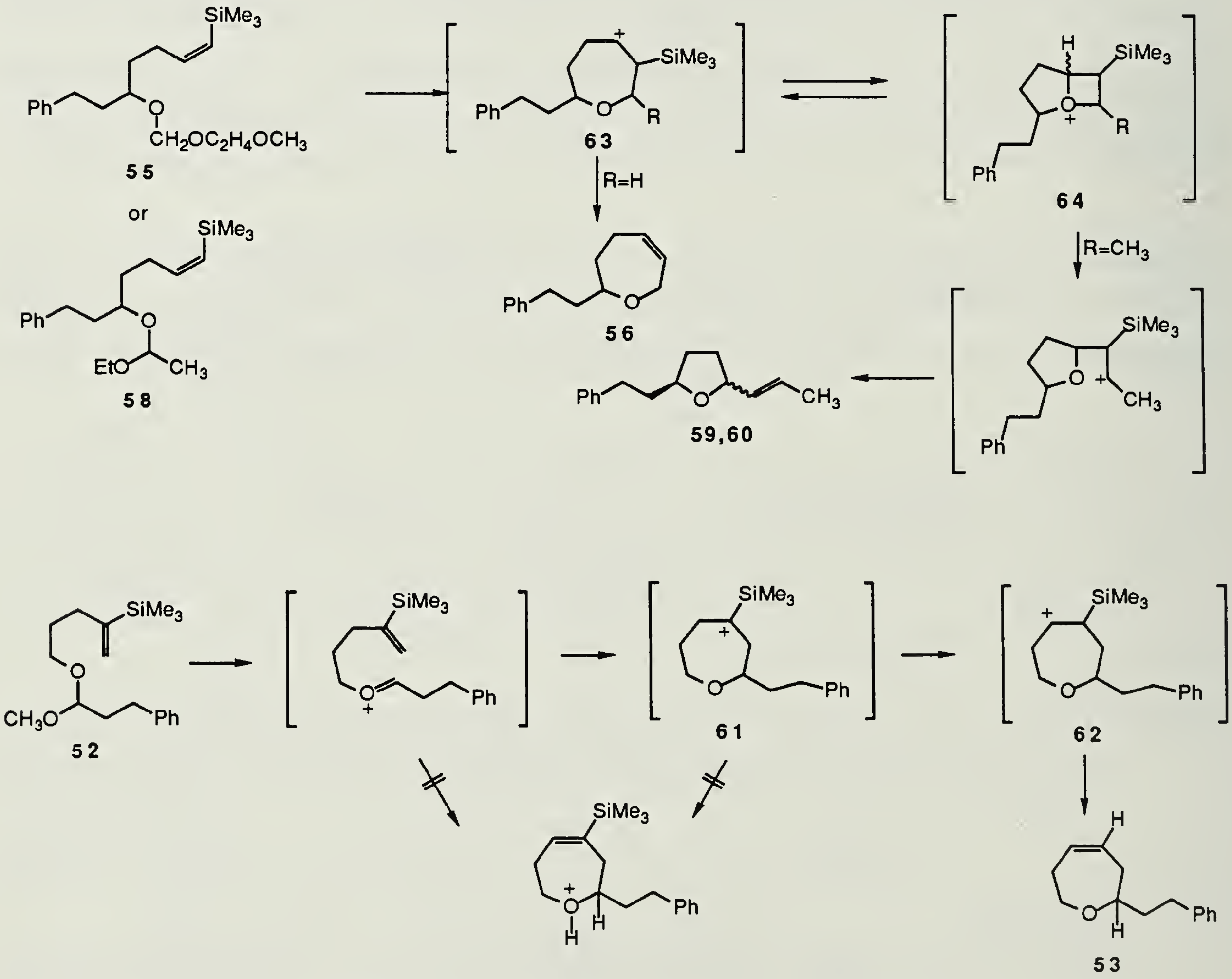


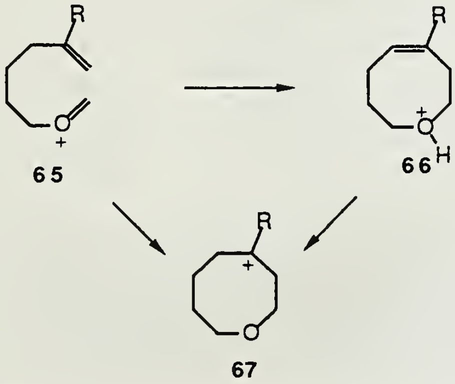
Possible mechanisms for the reactions are presented in Scheme 3. The cyclization of **52** yields Δ^4-oxepene products that do not contain the trimethylsilyl group because the initially formed Δ^4-oxepanyl cation, **61,** rapidly undergoes a 1,2-hydride migration to give the β-silyl cation isomer, **62**. The divergent behavior of vinylsilane acetals **55** and **58** can be understood on the base of the intervention of 1-oxabicyclo[3.2.0]heptanyl oxonium ion intermediates. That is, oxonium ion **64** would be more prone to cleavage of the 1-7 bond to afford a carbocation if R is a cation-stabilizing group such as CH_3 than if R is H. Thus, the formation of rearranged tetrahydrofuran product from **58** and not from **55** is reasonable.

Scheme 3

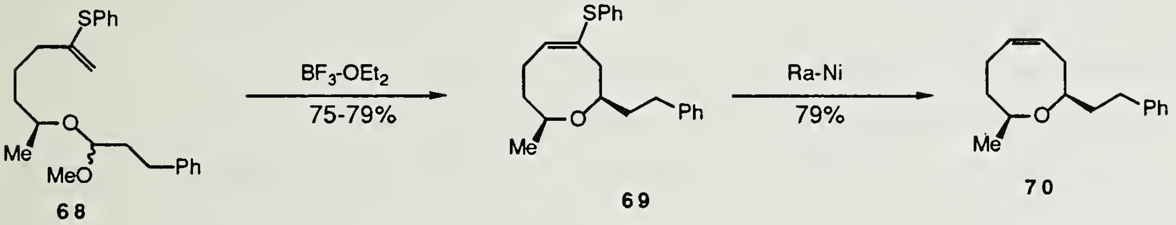


In 1990, Overman reported the preparation of eight-membered cyclic ethers by the Lewis acid-promoted cyclization of 5-alkenyl acetals.[23] His approach was suggested by earlier studies of thermal interconversion of octadiene and cis-cyclooctene.[24] The Alder ene cyclization of an oxocarbenium ion (oxonium ion) would form Δ^4-oxocene; and if the transformation of **65** to **66** took place in a stepwise fashion, initial endocyclization to form **67** would be facilitated by electron releasing substituents R which favor addition of electrophiles to the distal end of the 5-alkenyl double bond (Scheme 4).

Scheme 4



The reaction of MEM ether of 5-hexen-1-ol and $SnCl_4$ produces Δ^4-oxocene and 4-chlorooxocane in very low yield. Although, yields are low (20-40%) in the mixed acetals of 5-hexen-1-ol, the commercial availability of this alcohol and the fact that the cyclization can be conducted at practical concentrations (0.02-0.04 M) suggest that this simple approach to eight-membered ethers could be of use in some applications. To cause the cyclization to be more efficiently, 5-hexenyl acetals that have an electron releasing substituent at the internal alkene carbon were used. Electrophilic attack on 2-(trimethylsilyl)-1-alkene is known to form a tertiary α-silyl, rather than a primary β-silyl cation. After the cyclization, 4-(trimethylsilyl)-Δ^4-oxocene is afforded albeit still low yield (30-40%). Since an α-sulfenyl group is a more powerful carbenium ion stabilizing substituent than an α-silyl group, Lewis acid-promoted acetal-vinyl sulfide cyclizations were examined. The optimum diluent is *t*-butyl methyl ether and, in this solvent, the cyclization of **68** is remarkably clean and affords the sulfenyl oxocene **70** in yields of 75-79% (eq 17).

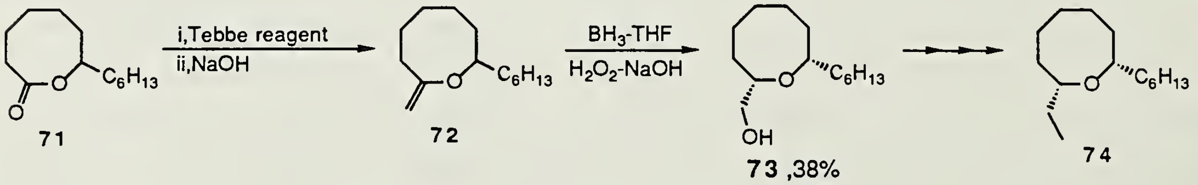


(17)

In summary, the yield of Δ^4-oxocene increases as the 5-substituent of a 5-hexenyl acetal is varied from H to $SiMe_3$ to SPh. Moreover, cyclization of vinylsilane or vinyl sulfide acetals derived from secondary alcohols proceeds with excellent (>25:1) stereoselectivity. The latter is presumed to stem from the E-oxocarbenium ion by an intramolecular ene mechanism proceeding via a boat-chair bicyclo[3.3.1]nonane transition state.

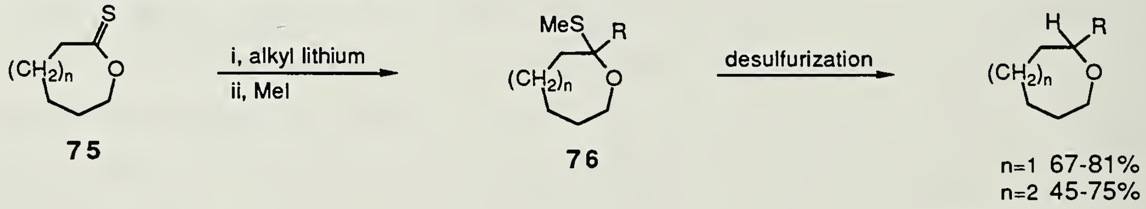
TRANSFORMATION OF LACTONES AND THIONOLACTONES

In 1986, Holmes reported the transformation of lactones to the corresponding cyclic ether by treatment with Tebbe reagent followed by hydroboration of the resulting enol ether (eq 18).[25] He used this method to make the cis-disubstituted oxocane, lauthisan, **74** (Tebbe reagent ; $(C_5H_5)_2Ti(\mu\text{-}CH_2,\mu\text{-}Cl)AlMe_2$).



(18)

Although the lactones are considered as excellent precursors to the corresponding ethers, nucleophilic additions to medium and large lactones result in rupture of the ring, due to the high reactivity of tetrahedral intermediates. By the report from Nicolaou in 1987, nucleophilic addition to thionolactone, **75**, was expected to lead to a more stable tetrahedral intermediate, and a facile S-alkylation of the intermediate afforded **76**. Futhermore, the methylthio group was easily removed by reduction with tin hydride (eq 19).[26]



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CAPTODATIVE RADICAL STABILIZATION: FACT OR FICTION

Reported by Michelle Baillargeon February 19, 1990

INTRODUCTION

The simultaneous substitution of an electron donating group and an electron withdrawing group on a radical center leading to a stabilization that is greater than the additive effects of the individual substituents has been termed captodative radical stabilization. During the past decade, there has been some controversy as to the amount and even the existence of such an effect[1,2] since quantitative values for thermodynamic stabilities of radicals have been difficult to obtain. Recently, Bordwell and co-workers[3] have developed a method for estimating relative radical stabilization energies from acidity constants and oxidation potentials. They have applied their methodology to radicals of the type $A\text{-}\dot{C}H\text{-}D$, where A is an electron acceptor and D is an electron donor, in order to test for the existence of the captodative effect.[4]

CAPTODATIVE EFFECT

Radical Stabilization

Steric and electronic effects of substituents on a radical center may affect both its thermodynamic and kinetic stability. Sterically demanding substituents tend to hinder approach to the radical center, thereby affording the radical an increased lifetime. This persistence is termed kinetic stabilization. Thermodynamic stability is achieved when substituents have the ability to delocalize the single electron and thereby reduce reactivity by reducing the spin density of the radical center. An intrinsic lowering of the radical ground state occurs. This stabilization has been defined in terms of dissociation energies of the R-H bond.

Carbocations are stabilized by electron donating substituents, while carbanions are stabilized by electron withdrawing substituents (Figure 1). Free radicals may be thermodynamically stabilized by either an electron donor or an electron acceptor.[5] When a free radical center possesses an electron accepting substituent (-CN, -COR, $-CO_2R$, NO_2 etc.), stability is obtained by the

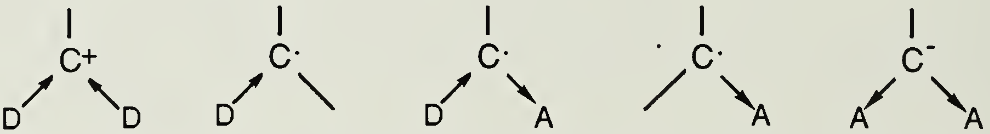

Figure 1. Stabilization of Carbocations, Radicals and Carbanions by Electron Donating (D) and Electron Accepting (A) Substituents

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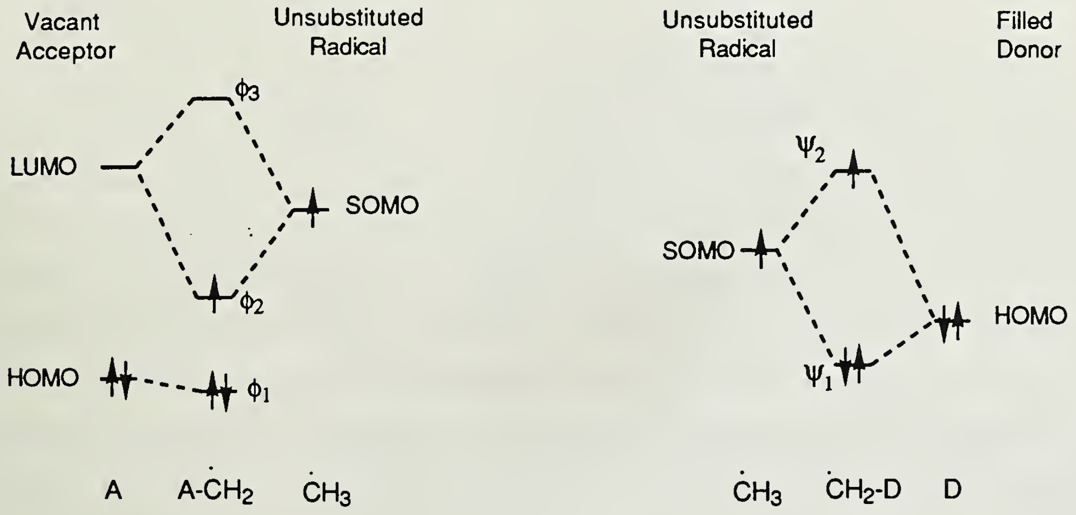
lowering of the singly occupied molecular orbital (SOMO) (Figure 2a). When a free radical center possesses electron donating substituent (-OR, -NR_2, -SR etc.), the resulting three electron interaction affords a stabilizing effect (Figure 2b). Two electrons are lowered in energy, while one is raised in energy.



(a) (b)

Figure 2. Important Orbital Interactions for Radical Stabilization by (a) an Electron Accepting Substituent and (b) an Electron Donating Substituent

Theory

It has been suggested that the simultaneous substitution of both an electron donor, D, and an electron acceptor, A, on a radical center leads to a stabilization that is greater than the sum of the individual stabilization energies. This enhanced stabilization is termed the captodative effect. Many theoretical calculations have been performed in an attempt to prove or disprove the existence of such an effect.[2] In terms of frontier orbitals, one may construct a correlation diagram for the captodative radical, A-$\dot{C}$H-D, by successive combination of the $\dot{C}H_3$ radical with an electron donor (Figure 2b) then an electron acceptor (Figure 3).[6]

The stabilizing interactions between a radical and a substituent increase as the orbital energies involved become closer. Substitution of a donor on the methyl radical results in a singly occupied orbital, Ψ_2, that is higher in energy than the unperturbed radical SOMO. The orbital energies are in the order LUMO A > SOMO > HOMO A. Therefore, the stabilization by an electron acceptor is more effective in the A-$\dot{C}$H-D captodative radical than in the A-$\dot{C}H_2$ monosubstituted radical. The A-$\dot{C}H_2$ radical has a lower energy SOMO than the unsubstitued methyl radical and as a result is closer in energy to the HOMO of the donor substituent D. The stabilization by an electron donor is predicted to be more effective in the captodative radical than in the D-$\dot{C}H_2$

monosubstituted radical. Thus, Viehe et al.[6a] predict that in the case of a radical with two substituents acting in unison, one donor and one acceptor, the overall radical stabilization energy should be greater than the sum of the individual substituents.

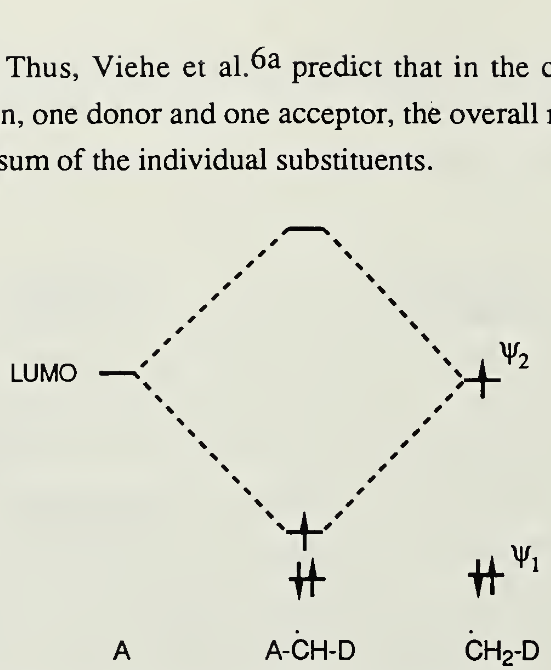


Figure 3. Orbital Energy Correlation Diagrams for the Captodative Effect $\dot{C}H_3$ with a Donor then an Acceptor

Schleyer et al.[6c] used unrestricted Hartree-Fock ab initio molecular orbital theory at the full geometry optimized split valence 4-31G basis set level to investigate the interaction of a π-donor and a π-acceptor bound to the same radical center. Their model system compared the $H_2N\dot{C}HBH_2$ radical with $NH_2\dot{C}H_2$ and $BH_2\dot{C}H_2$. They also considered the $NH_2\dot{C}HCN$ radical. The results of their calculations (Table I) indicate that a captodative effect of 3.4 and 12.3 kcal/mol was present in the $H_2N\dot{C}HCN$ and $H_2N\dot{C}HBH_2$ radicals respectively.

Table I. Stabilization Energies of Radicals

Radical	Stabilization Energy, kcal/mol[a]	Captodative Stabilization[b]
$H_2\dot{C}\text{-}BH_2$	10.9	-
$H_2\dot{C}\text{-}NH_2$	10.2	-
$H_2\dot{C}\text{-}CN$	12.5	-
$H_2N\text{-}\dot{C}H\text{-}BH_2$	33.4	12.3
$H_2N\text{-}\dot{C}H\text{-}CN$	26.1	3.4

[a]Based on $\dot{C}H_3$; $NH_2CH_2BH_2 + \dot{C}H_3 \text{-->} NH_2\dot{C}HBH_2 + CH_4$. [b]Stabilization in excess of the sum of the stabilizations of the individual substituents.

Katritzy et al.[7] estimated the synergistic effects of donor and acceptor substituents in A-ĊH-D radicals by theoretical INDO UHF calculations. Radicals of the captodative type allegedly allow delocalization of the radical over all of the atoms in the system. Therefore, solvation effects, expected to influence the importance of charge-separated resonance forms, were taken into account by the use of the self-consistent reaction field formulization. Katritzky suggests that the stabilization energy of the captodative radical be defined by equation 1. The calculations were

$$\Delta E_M = E_{A\text{-}D} - 0.5\,(E_{A_2} + E_{D_2}) \qquad (1)$$

referenced to the corresponding symmetrical radicals, $A_2\text{-}\dot{C}H$ or $\dot{C}H\text{-}D_2$. The second term in the equation is apparently a correction for saturation effects. A saturation effect occurs when the first substituent stabilizes the radical more than each additional substituent.[8] In an unsubstituted radical the odd electron is localized and gains more in stability by the addition of a substituent than does a radical in which the electron is already partly delocalized. The results that Katritzky obtained were different then those reported by Schleyer. No evidence for the captodative stabilization in $MeO\dot{C}HCN$ or $H_2N\dot{C}HCN$ radicals in the gas phase was found. In fact, Katritzky suggests that 1-5 kcal/mol destabilization occurs (Table II). However, the $A\text{-}\dot{C}H\text{-}D$ radicals were significantly more stable (7-28 kcal/mol) than the corresponding symmetrical radicals, $\dot{C}H\text{-}D_2$ and $A_2\text{-}\dot{C}H$, in solvents of high dielectric constant. The physical reason for this stabilization is the higher polarization (and dipole moment) of the donor-acceptor substituted radicals in a high delectric medium. The dipole moment of the symmetrically substituted radicals increases by only 15-20% as the dielectric constants increase from $\varepsilon = 1$ to 80. The corresponding change for the

Table II. Calculated Properties of Radicals[a]

Radical	Dielectric Constant of Solvent	Total Energy (hartree)	Rel Energy (kcal/mol)	Dipole Moment (D)	ΔE_M [b] (kcal/mol)
$\dot{C}H(CN)_2$	1	-40.70469	(0)	2.842	
	80	-40.72648	-13.7	3.511	
$\dot{C}H(OH)_2$	1	-41.72964	(0)	0.889	
	80	-41.73299	-2.1	1.006	
$\dot{C}H(OCH_3)_2$	1	-57.83485	(0)	3.392	
	80	-57.85873	-15.0	3.853	
$\dot{C}H(NH_2)_2$	1	-30.84759	(0)	2.840	
	80	-30.87065	-14.4	3.314	
$HO\dot{C}HCN$	1	-41.21226	(0)	3.279	3.1
	80	-41.26855	-35.5	5.168	-24.4
$H_3CO\dot{C}HCN$	1	-48.91932	(0)	4.341	1.2
	80	-48.99797	-49.4	6.796	-28.8
$H_2N\dot{C}HCN$	1	-35.76695	(0)	3.150	5.7
	80	-35.81012	-27.1	5.039	-7.3

[a] INDO UHF Self-Consistent Reaction Field

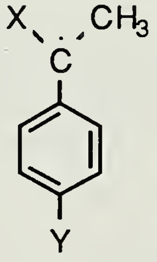
[b] Calculated as per equation 1 using total energies in hartree then converted to kcal/mol.

captodative radicals is 50-60%. Katritzky et al. suggest that captodative stabilization of radicals in solution is essentially casused by environmental effects on their electronic structure and stability.

EXPERIMENTAL ARGUMENTS: DOES THE CAPTODATIVE EFFECT EXIST?

Results of Viehe and Co-Workers

In general, thermodynamically stabilized radicals are not persistent. However, De Vries and co-workers reported remarkable persistence for the dicyano(dimethylamino)methyl radical.[9] Viehe and co-workers attempted to explain the behavior of this radical by the electronic effects of the polar substituents.[6a] They claimed that a captodative effect was operating because there were no apparent steric effects playing a determining role. However, this radical has two electron accepting cyano substituents and is not strictly a $A\text{-}\dot{C}H\text{-}D$ system. Viehe and co-workers did not perform actual experiments on the dicyano(dimethylamino)methyl radical. Instead they based their conclusions on electron spin resonance experiments with benzylic radicals, **1**.[10] In the these experiments a freely rotating methyl group served as a probe for the benzylic carbon spin density.



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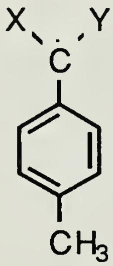

2

The donor or acceptor was placed in the para position on the benzene ring to eliminate steric interactions. Variations in the β-hyperfine splittings of the methyl proton, $a_H^{CH_3}$, reflect changes in the spin delocalization. An increased spin delocalization indicates an increased radical stabilization. An experimental delocalization parameter, S_{XY}^{exptl}, is defined for each set of substituents, X and Y (eq 2). For the unsubstituted benzylic radical S_{HH}^{exptl} is zero and the

$$S_{XY}^{exptl} = 1 - (a_{XY}/a_{HH}) \qquad (2)$$

value increases with the stabilizing power of the substituents. The data in Table III indicate that the stabilization contributed by the captodative substitution is greater than those contributed by either two acceptor or two donor substituents. The S^{calcd} value represents the superimposition of the individual effects for the disubstituted radical (eq 3). These values are greater than the corresponding experimental values in the cases in which two substituents are the same.

$$S_{XY}^{calcd} = 1 - (1 - S_{XH}^{exptl})(1 - S_{HY}^{exptl}) \qquad (3)$$

However, the S^{calcd} are smaller than S^{exptl} for the captodative radicals. The ΔS (eq 4) represents a synergetic effect if positive and an antagonistic effect if negative. The effects are

$$\Delta S = (S_{XY}^{exptl} - S_{XY}^{calcd}) / S_{XY}^{calcd} \qquad (4)$$

stronger when X and Y are directly bonded to the radical center as in the benzylic radicals, **2**.

Table III. Hyperfine Coupling Constants and Delocalization Parameters in Benzylic Radicals

Radical	X	Y	$a_H^{CH_3}$, G	S_{XY}^{exptl}	S_{XY}^{calcd}	ΔS, %
1a	H	H	17.70	0		
1b	H	OMe	17.25	0.025		
1c	H	CN	16.90	0.045		
1d	CN	H	16.10	0.090		
1e	CN	CN	15.90	0.102	0.131	-22
1f	OMe	OMe	15.75	0.110	0.146	-25
1g	OMe	H	15.50	0.124		
1h	CN	OMe	14.85	0.161	0.113	+42
1i	OMe	CN	13.95	0.212	0.163	+30
2a	H	H	6.53	0		
2b	OMe	OMe	6.40	0.020	0.0183	-89
2c	H	CN	5.92	0.093		
2d	H	OMe	5.90	0.096		
2e	CN	CN	5.90	0.096	0.177	-46
2f	CN	OMe	4.44	0.320	0.180	+78

Results of Bordwell and Co-Workers

In the mid 1970's, Bordwell et al.[11] established a titration method which uses colored organic anions as indicators to determine acidity constants, pK_a values, of carbon acids in dimethyl sulfoxide (DMSO). This technique involves relating the acidity of two acids, in which the pK_a of one is known, by titrating one with the other. The method requires that one acid have a colored anion and that the other have either a colorless anion or one that absorbs at a different wavelength. The equilibrium position of the unkown acid is determined from the concentrations of the two acid solutions and by measuring the concentration of the colored anion spectrophotometrically after each addition of titrant.

The most recent application of Bordwell's pKa scale has been to combine acidity values with the oxidation potentials of the corresponding anions to obtain estimates of relative homolytic bond dissociation energies (BDE), which in turn provide estimates of relative radical stabilities. The thermochemical cycle shown in equations 5 to 8 provides the theoretical basis for these estimates.[3] The E_{ox} (A^-) is measured by cyclic voltammetry, and the E_{red} (H^+) is taken as a constant when comparing families of acids. The differences in the sum of the oxidation potentials and the acidity constants, both measured in DMSO and expressed in kilocalories per mol, may be

$$\begin{array}{llll}
HA \rightleftharpoons H^+ + A^- & & pK_{HA} & (5) \\
A^- \rightleftharpoons e^- + A^{\cdot} & & E_{ox}(A^-) & (6) \\
\underline{H^+ + e^- \rightleftharpoons H^{\cdot}} & & E_{red}(H^+) & (7) \\
HA \rightleftharpoons H^{\cdot} + A^{\cdot} & & BDE & (8)
\end{array}$$

taken as measures of relative bond dissociation energies or relative radical stabilization energies (eq 9).[3] This is based on the assumption that the differences in ground state energies of acids

$$\Delta BDE = \Delta pK_{HA} + \Delta E_{ox}(A^-) \qquad (9)$$

of similar structure are small when compared to differences in their homolytic bond dissociation energies. The extent of irreversibility of the oxidation of many anions has been similar enough within families of anions to permit estimates of relative bond dissociation energies and of relative radical stabilization energies by this method.

Since the dicyano(dimethylamino)methyl radical was cited as being very persistent and that this persistence was due to a captodative effect, Bordwell and co-workers tested for the alleged effect by their methodology.[4] They examined the radical stabilization eneergies of $H_2N\dot{C}(CN)_2$ and $Me_2N\dot{C}(CN)_2$ (Table IV). Both α-H_2N and α-Me_2N groups exert 16 kcal/mol stabilizing effect when substituted for a hydrogen atom in$(CN)_2\dot{C}H$ radicals. This value is 5 kcal/mol less than that obtained for the radical stabilization energy of the $Me_2N\dot{C}H_2$ radical.

Table IV. Stabilization Energies of Radicals Derived from Subsituted Dicyano Methyl Radicals, $G\dot{C}H(CN)_2$, in DMSO at 25°C

G	pK_{HA}	E_{ox} (A^-)	RSE
H	11.0	0.938	(0.0)
H_2N	13.7	0.088	16
Me_2N	12.2	0.180	16

Bordwell also found that the oxidation of the $(CN)_2C(NMe_2)^-$ anion is reversible, while the oxidation of the $(CN)_2C(NH_2)^-$ is irreversible. The reversible oxidation indicates that the radical formed by the loss of an electron has a sufficient lifetime on the electrode to be reduced to the carbanion. It was suggested that the steric effect introduced by replacing the hydrogen atoms of the H_2N group by methyl groups leads to the persistence of the radical.[12]

Bordwell also examined α-substituted acetophenone systems for captodative effects (Table V). The estimated effects for the methoxy and ethoxy substituted acetophenone are 12.9 +/- 2

Table V. Radical Stabilization Energies for Radicals Derived from α-Subsituted Acetophenones, $PhCOCH_2R$

R	pK_{HA}	E_{ox} (A-)	RSE
H	24.7	0.268	(0.0)
OMe	22.85	-0.175	13.1
OEt	22.9	-0.167	12.9
NH_2	~24	-0.650	~22
NMe_2	23.55	-0.610	21.6
$c\text{-}C_5H_{10}N$	23.5	-0.564	21
$2,6\text{-}Me_2\text{-}c\text{-}C_5H_8N$	22.8	-0.405	18.5

and 13.1 +/- 2 kcal/mol, respectively, relative to the $PhCO\dot{C}H_2$ radical. These effects are only slightly larger than the effect of OMe in the $MeO\dot{C}H_2$ radical (12 kcal/mol). Therefore, Bordwell concludes that the effects of MeO and PhCO in the $Me\dot{C}HCOPh$ radical are approximately additive. The radical stabilization energies for $R_2N\dot{C}HCOPh$, relative to the $PhCO\dot{C}H_2$ radical are ~21 kcal/mol. These effects are the same as the effect of Me_2N in the $Me_2N\dot{C}H_2$ radical (21 kcal/mol). There is no evidence for the existence of a captodative effect by this criterion.

Since Katritzky had reported that saturation effects should be accounted for, Bordwell presented evidence to illustrate intrinsic (gas phase) saturation effect on ΔBDEs (Table VI). The effect on the relative bond dissociation energy by a second methyl substitution onto methane is ~40% (4/7) as large as the first, while a third methyl substitution is ~30% (2/7). An effect of ~50% occurs when a second vinyl is substituted onto methane. The effect of the second phenyl substitution onto methane is only ~25% as large as the first, but here steric inhibition of

Table VI. Examples of Intrinsic Saturation Effects on ΔBDEs

Compound	BDE	ΔBDE	ΔΔBDE	ΔΔΔBDE
CH_3-H	105	(0.0)		
$MeCH_2$-H	98	7	(0.0)	
Me_2CH-H	95		3	(0.0)
Me_3C-H	93			2
CH_3-H	105	(0.0)		
CH_2=$CHCH_2$-H	86	19	(0.0)	
$(CH_2$=$CH)_2CH$-H	76		10	
CH_3-H	105	(0.0)		
$PhCH_2$-H	88	17	(0.0)	
Ph_2CH-H	84		4	(0.0)
Ph_3C-H	82			2

delocalization in the radical also plays a role. The system must be coplanar for maximum conjugation, but the ortho-hydrogen atoms of the adjacent rings interfere sterically and prevent the preferred coplanarity.

Another example (where steric effects are minimal) can be seen by comparing the radical stabilization energies of the 9-methyl fluorenyl (9-MeFl·) and 9-CNFl· radicals, relative to the 9-HFl· radical, with those of $Me\dot{C}H_2$ and $\dot{C}H_2CN$ radicals relative to the methyl radical (Table VII).

Table VII. Comparision of Radical Stabilization Energies of 9-Substituted Fluorenyl and Substituted Methyl Radicals

G	RSE (9-G-Fl·)	RSE (GCH_2·)
H	(0.0)	(0.0)
Me	4.5	7
CN	5.7	12

The larger radical stabilization energies for the latter radicals are due to the localized nature of the $\dot{C}H_3$ radical, causing it to have a maximum sensitivity to delocalization provided by the substituents. The radical stabilization energy of Me in 9-MeFl· is ~64% (4.5/7) of that of Me in $Me\dot{C}H_2$ and that of CN in 9-CNFl· is only ~50% (5.7/12) of that of CN in $\dot{C}H_2CN$ radical. The gas phase acidifying effect of the second CN group in the series CH_4, CH_3CN, $CH_2(CN)_2$ is subject to a 25% saturation effect.[13] Based on these examples Bordwell assumed a conservative 25% saturation effect for the substitiution of an α-MeO or α-Me_2N group for an α-hydrogen atom in the $PhCO\dot{C}H_2$ radical. The acetophenone systems are examined for the captodative effect after such saturation effects are considered. The radical stabilization energy for $PhCO\dot{C}H_2$ relative to $\dot{C}H_3$ is estimated to be 12 kcal/mol. To this is added the observed 13 kcal/mol stabilizing effect for the methoxy group when it replaces one of the α-H in the $PhCO\dot{C}H_2$ radical and 25% of this value to account for the saturation effect. From this sum the radical stabilization energy for $PhCO\dot{C}H_2$ and $MeO\dot{C}H_2$ relative to $\dot{C}H_3$ (each 12 kcal/mol) are subtracted, [12 + 13 + (.25 X 13)] - (12 + 12). A synergistic effect of at least 4 kcal/mol is calculated for the PhO and α-MeO groups. In a similar manner, [12 + 21 + (0.25 X 21)] - (12 + 21), a synergistic effect of 5 kcal/mol is calculated to be operating in the $PhCO\dot{C}HNR_2$ system.

CONCLUSION

There has been considerable interest in the question of whether or not simultaneous substitution of an electron acceptor and donor on a radical center causes the substituents to act synergistically to provide stabilization greater than expected for the individual effects. Both theoretical and experimental arguments have been reported in support of and in opposition to the captodative effect. Schleyer presented theoretical calculations indicating that a captodative effect exists. Katritzky attributes these effects to solvation. Viehe attributed the stabilization of the dicyano(dimethylamino)methyl radical to captodative effects. However, this radical has two cyano groups and is not strictly an A-$\dot{C}$H-D system. Bordwell presented evidence against the captodative effect as defined by Viehe. However, if saturation effects are considered, Bordwell suggests that synergetic effects of donor and acceptor groups do operate in such radicals. The data reported to date on the alleged captodative effect is inconclusive.

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CHIRAL LITHIUM AMIDES: VERSATILE REAGENTS FOR ASYMMETRIC SYNTHESIS

Reported by William E. Bowen February 22, 1990

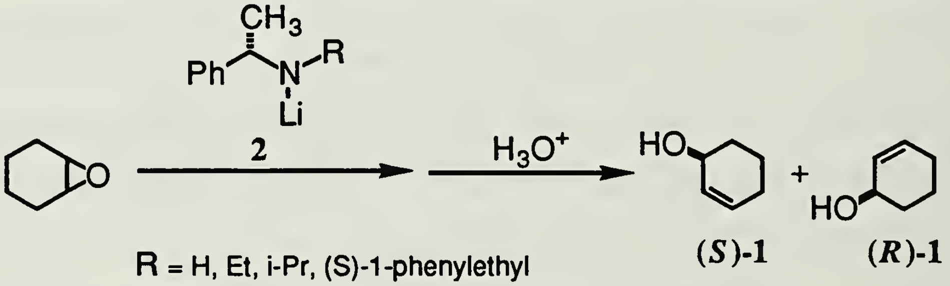
INTRODUCTION

In the last decade, asymmetric methodology has intensely interested organic chemists. The use of either covalently bound chiral auxiliaries or complex organometallic reagents are two well known methods for introducing a stereogenic center into an achiral substrate. However, the use and synthesis of these reagents is often difficult. The availability of a number of chiral amines and the ability of lithium amides to act not only as strong bases but also as chiral auxiliaries made these amides likely candidates for study. Thus, chiral lithium amides have been explored as versatile and simple-to-use reagents for asymmetric induction.

DEPROTONATION

Epoxides

In 1980, Whitesell and Felman reported the use of chiral lithium amides to differentiate between enantiotopic protons in cyclohexene oxide (eq 1).[1] The experiment consists of the selective deprotonation of the epoxide to yield optically active (*R*) or (*S*)-2-cyclohexene-1-ol (**1**).



(1)

Moderate enantiomeric excesses (e.e.) (3-31% e.e.) were obtained using chiral lithium amides derived from (*S*)-1-phenylethylamine (**2**). Whitesell proposed that a complex aggregation of the lithium amide in solution was responsible for the observed asymmetric induction.

Asymmetric deprotonation of cyclohexene oxide to yield allylic alcohols has been rigorously studied by Asami[2-5] who used chiral lithium amides derived from (*S*)-proline (3). Deprotonation of the epoxide followed by acidic workup yields optically active (*S*)-2-cyclohexene-1-ol ((*S*)-**1**) with high e.e. (Table I, entries 1-6).

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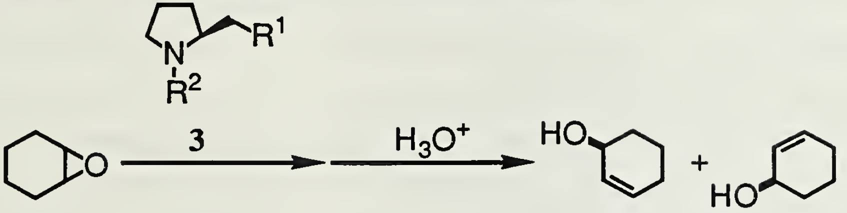
Table I. Asymmetric Transformation of Cyclohexene Oxide.

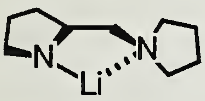


(*S*)-1 (*R*)-1

Entry	R^1	R^2	Yield(%)	Conf.	e.e.(%)
1	pyrrolidinyl	Li	78 (77)[a]	*S*	90 (92)[a]
2	piperidinyl	Li	71	*S*	81
3	morpholinyl	Li	70 (72)[a]	*S*	86 (88)[a]
4	4-(Me)piperazinyl	Li	67	*S*	68
5	$N(Et)_2$	Li	69	*S*	83
6	N(Me)Ph	Li	55	*S*	47
7	$LiN(C_6H_5)$	Me	85	*R*	62
8	$LiN(C_6H_5)$	Et	80	*R*	78
9	$LiN(C_6H_5)$	i-Pr	75	*R*	57
10	$LiN(C_6H_5)$	t-Bu	63	*S*	39
11	$LiN(C_6H_5)$	n-Pent	77	*S*	62

[a] Runs made at 0 °C as opposed to the standard temperature of -78 °C.

Asami proposed that the base forms a tight five-membered cyclic complex, **4**, between the lithium and the amine terminus in solution. The deprotonation of cyclohexene oxide has been shown to be selective for the syn protons.[6] Enantiodifferentiation of the prochiral protons is believed to arise through a six-membered chair transition state. The proposed diastereomeric transition states, **5** and **6**, illustrate how the amide differentiates between the enantiotopic protons. Asymmetric induction arises from steric interaction of the amine terminus of the lithium amide with the cyclohexane ring. The preferred transition state, **6**, limits steric interactions between the pyrrolidine and cyclohexane rings resulting in an allylic alcohol of the *S* configuration.



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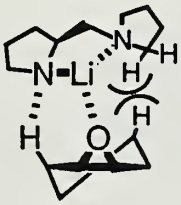

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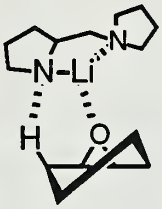

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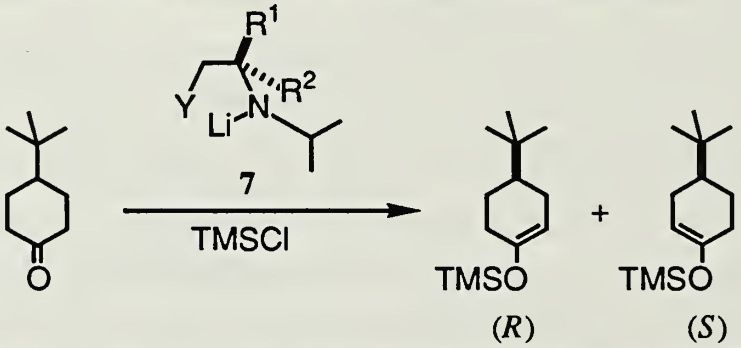
Asami complemented the formation of (*S*)-2-cyclohexene-1-ol (*S*)-**1** with an alternative method for producing the *R* enantiomer.[4] A series of chiral lithium amides was synthesized with increasing steric bulk on the proline nitrogen and substituting a cyclohexyl increasing steric bulk on the proline nitrogen and substituting a cyclohexyl group on the aliphatic portion of proline (Table I, entries 7-11). Lithiation occurs on the non-proline nitrogen. Reaction with cyclohexene oxide to form the allylic alcohol proceeds with moderate e.e. A reversal in the stereochemical preference is observed when the substituent on the non-proline nitrogen is sterically formidable (Table I, entries 10, 11). Asami has preferentially formed both enantiomers of chiral allylic alcohols from cyclopentene oxide and cyclooctene oxide. Application of Asami's chiral lithium amides to acyclic systems has proven feasible. (*Z*)-2-Butene oxide and (*Z*)-4-octene oxide were enantioselectively converted to their allylic alcohols in moderate e.e.'s (59-70% e.e.). Transition state models similar to those employed in cyclic cases were applied to the acyclic systems.

Ketones

Chiral lithium amides have been extensively studied for the selective deprotonation of prochiral ketones.[7] Koga developed chiral lithium amides derived mainly from (*R*)-phenylglycine (Table II).[8-10] The amine function is substituted with an isopropyl group while

Table II. Enantioselective Deprotonation of 4-*tert*-Butylcyclohexanone.

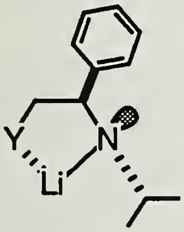


Entry	R^1	R^2	Y	Yield(%)	Conf.	e.e.(%)
1	Ph	H	OMe	90	*R*	47
2	t-Bu	H	OMe	91	*R*	39
3	H	i-Pr	OMe	88	*S*	26
4	H	Bn	OMe	65	*S*	36
5	Ph	H	$N(Me)_2$	35	*R*	51
6	Ph	H	pyrrolidenyl	52	*R*	73
7	Ph	H	piperidenyl	67	*R*	84
8	Ph	H	4-(Me)piperazinyl	87	*R*	84
9	Ph	H	4-(Me)piperazinyl	51	*R*	97[a]
10	H	Ph	H	63	*S*	70

[a] Run made at -105 °C as opposed to standard the temperature of -78 °C.

the carboxylic acid function is substituted with a group capable of chelation to lithium. Enantioselective deprotonation of 4-*tert*-butylcyclohexanone by the lithium amide and subsequent formation of the TMS enol ether were studied. Either enantiomer can be preferentially formed in moderate to high e.e. As one would expect, a reversal in the configuration of the TMS enol ether is observed when the configuration of the lithium amides stereogenic center is inverted (Table II, entries 3,4). Movement of the stereogenic center to the position beta to the amine greatly lowers the e.e. Furthermore, no change in the enantiomer formed is observed when the opposite configuration at the beta position is used.

Koga proposed a "working hypothesis" for the reaction mechanism. Koga's mechanism relies on a five-membered cyclic chelated structure, **8**. The five-membered cyclic chelate **8** is consistent with similar complexes proposed by Asami.[3] The structure of the amine in the complex is believed to be such that the isopropyl group is trans to the more sterically bulky R^1 or R^2 (Table II). Thus, the nitrogen lone pair resides cis to the more sterically cumbersome R^1 or R^2. Koga considered the reactions to be formally 1,4-asymmetric inductions but actually controlled by 1,2-asymmetric induction from the formation of a chiral nitrogen. Deprotonation of the cyclohexanone occurs axially with the *t*-butyl substituent in the equatorial position. Six-membered transition states **9** and **10** were proposed with coordination of lithium to oxygen and nitrogen abstraction of a proton both occurring on the same face of the ring. Violation of this "same side" coordination model results in a transition state that can not go through a six-membered alignment. Structures **9** and **10** were proposed as enantiodifferentiating transition states. Transition state **9** was believed to be preferred from evaluation of non-bonded interactions.



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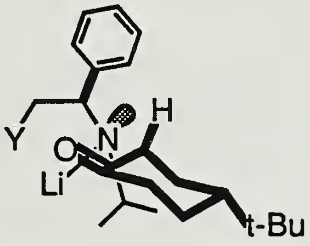

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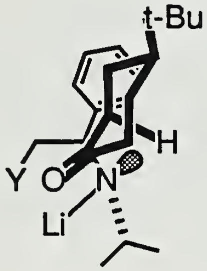

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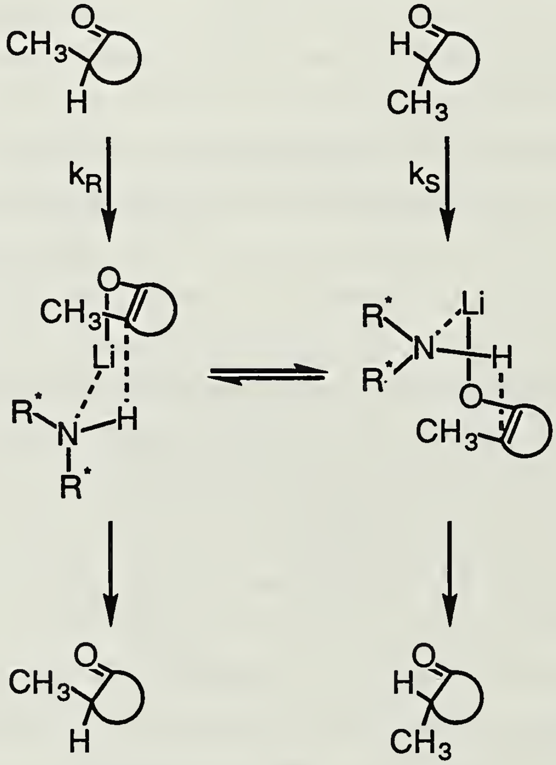
Koga's model has a curious anomaly. Substitution resulting in the removal of the chelation site on the lithium amide does not strongly influence the enantioselectively (Table II, entry 10). Thus, bases of this type could prove valuable owing to their ready accessibility.

Selective deprotonation of racemic 2,2,6-trimethylcyclohexanone was studied by Hogeveen.[11,12] Lithium bis[(*S*)-1-phenylethyl]amide was used as the chiral base. Selective deprotonation and reformation of the ketone by acid hydrolysis results in 2-46% e.e. The general scheme for the reaction was examined. Hogeveen proposed the existence of diastereomeric lithium enolate chiral amine complexes (Scheme I). Complexes were hypothesized because carbanion-amine complexes have been reported. Quenching of the lithium enolate with 1N DCl in D_2O leads to products free of deuterium; carboxylation and benzylation of the enolate were shown to proceed enantioselectively.

Scheme I

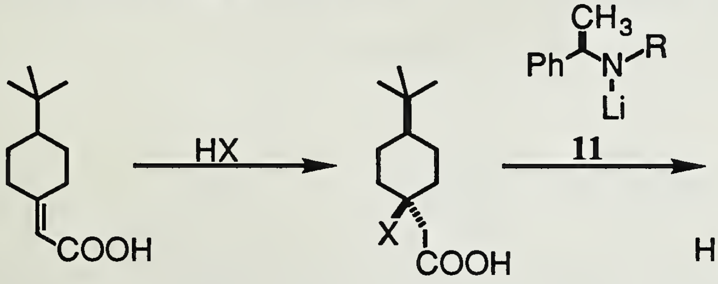


It was suspected that the asymmetric induction is dependent on the rate of deprotonation of the two enantiomers. Enantiomerically enriched starting material (15% e.e.) was subjected to the reaction conditions and yielded a further enriched sample (28% e.e.). Thus, k_R is not equal to k_S. In addition, a standard condition for deprotonation is a gradual rise (30 min) from -80 to -40 °C. Holding the deprotonation temperature constant at 0 °C or -80 °C leads to optically inactive products. It was assumed that at 0 °C deprotonation is complete and at -80 °C no deprotonation occurs. Under the reaction conditions, it was determined that only 40% of the compound is deprotonated. Hogeveen concluded that the observed enantioselectivity is due exclusively to kinetic resolution. Furthermore, a 50% e.e. was hypothesized as the theoretical maximum for the studied reaction.

α-Deprotonation of Carboxylic Acids

The enantioselective α-deprotonation of carboxylic acids and esters has been an active area of research.[13] Duhamel has studied the deracemization of methyl *N*-benzylidene phenylglycinate.[14] Deprotonation of the methyl ester by a chiral lithium amide and reprotonation of the lithium enolate with a chiral acid yielded optically active products. Lithium *N*-substituted (1-phenylethyl)amides were examined as chiral bases. Isomers of diacyltartaric acids were used as chiral acids. Exclusion of the chiral acid as the proton source lowers the e.e., but asymmetric induction is still observed. The best result (70% e.e.) is obtained with lithium *N*-ethyl-[(*S*)-1-phenylethyl]amide and (2*R*, 3*R*) dipivaloyltartaric acid. Duhamel proposed that the asymmetric induction is possibly caused by the chiral amine set free from the lithium amide but did not elaborate upon this hypothesis.

Duhamel examined a system to deracemize 4-*tert*-butyl-cyclohexylidene acetic acid through a selective dehydrohalogenation step (eq 2).[15] The racemic acid was hydrohalogenated to give the prochiral β-halo carboxylic acid. Subsequent enantioselective dehydrohalogenation yields optically active 4-*tert*-butyl-cyclohexylidene acetic acid with 8-82% e.e. The chiral bases studied were *N*-substituted derivatives of 1-phenylethylamines **11**. Either enantiomer of the acid can be obtained preferentially by altering the steric bulk of the R group. Holding the R constant, substitution of naphthyl, cyclohexyl, or methylpinane for the phenyl in the chiral phenylethylamine moiety decreases enantiomeric excesses.



(2)

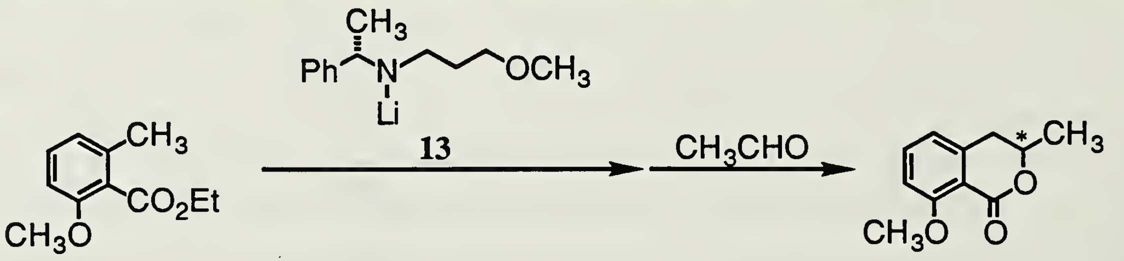
R = Me, Et, Pr, i-Pr, Bn, t-Bu,
n-Pent, CH_2(1-adamantyl)

CARBON-CARBON BOND FORMATION

Aldol-type Reactions

The formation of the carbon-carbon bond is of fundamental importance to organic chemistry. Accordingly, the selective formation of carbon-carbon bonds has been an area of intense study.[16]

The asymmetric synthesis of mellein methyl ether (**12**) has been reported by Staunton and Regan (eq 3).[17] This synthesis was accomplished through selective formation of the benzylic carbanion from an ortho-toluate through the use of lithium *N*-3-methoxypropyl-[(*S*)-1-phenylethyl]amide (**13**) as the base. Subsequent condensation of this anion with acetaldehyde gave mellein methyl ether of 55% e.e. In a follow-up study,[18] the condensation of acetone with a phenylethyl carbanion (generated by the base **13**) was found to yield bicyclic lactone **14** of 72% e.e. (eq 4). Similar attempts to condense the toluate ester with acetaldehyde gave a 3:1 ratio of the *cis* and *trans* lactones in 70 and 74% e.e. respectively . The *trans* lactone was carried on to the synthesis of citrinin.



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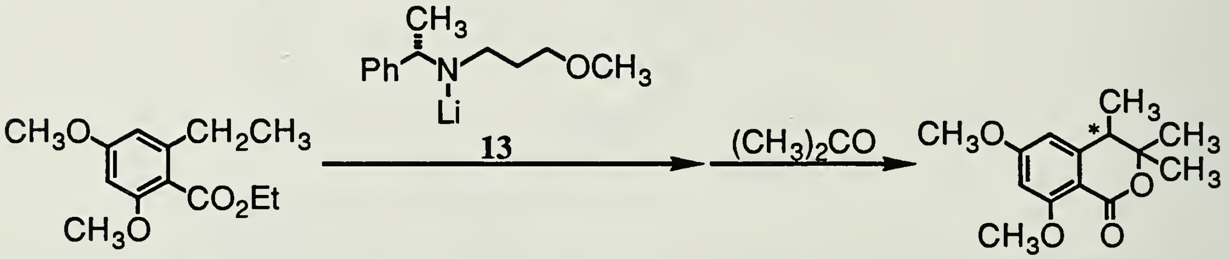

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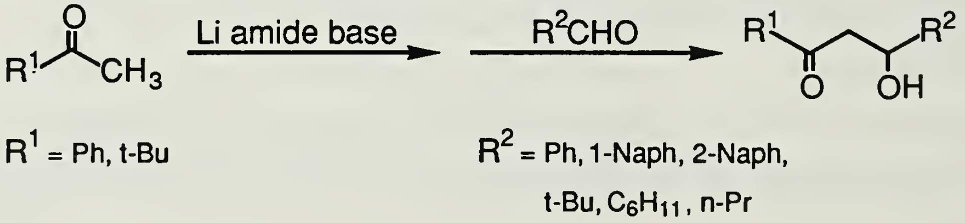
(4)

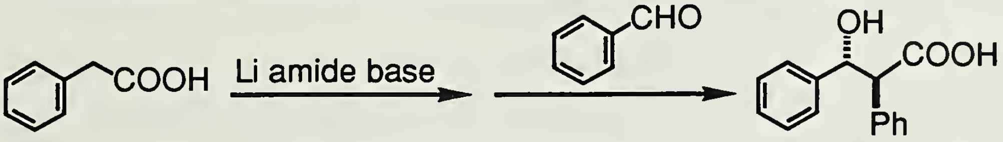
Koga has applied the bases he earlier used in the deprotonation of ketones to the condensation of methyl ketones with aldehydes (eq 5).[19] The methyl ketones were deprotonated by the chiral bases and the aldehyde was subsequently added. The β-hydroxy ketones so obtained were observed to have enantiomeric excesses from 50-86% under optimized conditions. No transition structure hypothesis has been proposed, but Koga implies that the 5-membered chelated cycle is important for asymmetric induction.



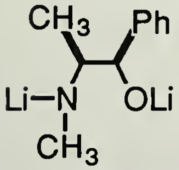
(5)

Mulzer and co-workers examined the asymmetric addition of phenylacetic acid to benzaldehyde (Table III) using a variety of chiral lithium amides (**15-19**) to form the phenylacetic acid dianion.[20] These lithium amides all have one or more lithium alkoxide groups.

Table III. Enantioselective Addition of Benzaldehyde to Phenylacetic acid.



Base	Yield(%)	Conf.	e.e.(%)
15	85	2*S*, 3*R*	58
16	80	2*R*, 3*S*	43
17	87	2*S*, 3*R*	31
18	83	2*S*, 3*R*	31
19	80	2*S*, 3*R*	85
15 + TMSCl	82	-	0



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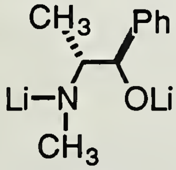

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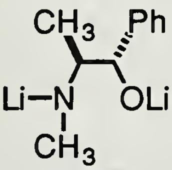

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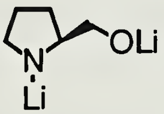

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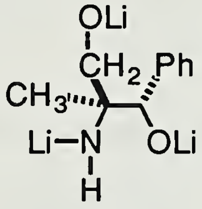

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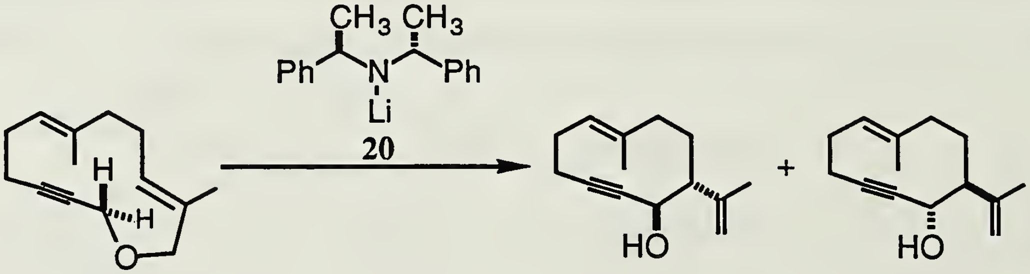
Comparison of the results obtained using bases **15** and **16** indicates that asymmetric induction arises from the stereogenic center alpha to the lithiated nitrogen, rather than the beta stereo center. This is in agreement with Koga's findings for the enantioselective deprotonation of ketones.[7] Trianionic base **19** affords the greatest e.e. (85%) obtained in the study. Mulzer suggested that the additional OLi site enhances the rigidity of the chiral enolate complex. Lithiation of the amine precursor of **15** with trimethylsilyl chloride (TMSCl) present is believed to form the O-trimethylsilyl lithium amide (i.e. **15** with OTMS substituted for OLi). Subsequent reaction of this lithium amide with phenyl acetic acid and subsequent addition of benzaldehyde results in non-optically active condensation products. Silylation of the OLi site is believed to be responsible for the loss in asymmetric induction. Thus, the amine is responsible for deprotonation, but the OLi moieties are necessary for asymmetric induction.

[2,3] Wittig Rearrangement

Marshall and co-workers have initiated [2,3] Wittig rearrangements of allylic ethers through the use of chiral lithium amides.[21,22] [2,3] Wittig ring contractions often exhibit high diastereoselectivity but lead to racemic products. Lithium bis[(*S*)-1-phenylethyl]amide (**20**) and its enantiomer were used as chiral bases for [2,3] Wittig ring contractions on a 13-member acetylenic cyclic ether substrate **21** (eq 6). As expected, changing the configuration of the amide



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(6)

leads to preferential formation of the opposite enantiomer. Enantiomeric excesses of 69% and 70% were observed for the (*S*, *S*) and (*R*, *R*) amides respectively. Similar attempts to conduct enantioselective [2,3] Wittig ring contractions on a 17-membered allylic propargylic ether are not as successful, resulting in a 33% e.e. when the (*S*, *S*) base is used. Likewise, attempts at enantioselective Wittig rearrangements on acyclic allylic ethers give primarily non-optically active products.

CONCLUSION

Chiral lithium amide bases are versatile reagents for introduction of chirality into achiral substrates. These bases are readily available, simple to use, and often afford substantial degrees of asymmetric induction. Chiral lithium amides derive their utility from their ability to act as both strong non-nucleophilic bases and chiral auxiliaries. Transition state models have been proposed to account for the selectivities observed with these bases but are rather speculative in nature.

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INTERMOLECULAR HOMOGENEOUS ACTIVATION OF ALKANE CARBON-HYDROGEN BONDS BY TRANSITION METAL COMPLEXES

Reported by Jeanine Shusta February 26, 1990

INTRODUCTION

Alkanes are among the most abundant, yet unreactive of all organic compounds. As major constituents of natural gas and petroleum, alkanes are very attractive feedstocks for the synthesis of organic compounds. Unfortunately however, the relatively unreactive character of simple alkanes precludes their usefulness in organic synthesis. Unstrained alkanes lack both lone pairs and empty orbitals. Carbon-hydrogen bonds are difficult to cleave owing to their low polarity and high bond strengths. The strong bonding between carbon and hydrogen means that the HOMO's are low lying σ-bonding orbitals and the LUMO's are high lying σ-antibonding orbitals, neither of which is easily accessible to an attacking reagent.

Saturated hydrocarbons have a long history of activation by nonmetallic reagents and methods. Hydrocarbon thermal reactions and combustion have been studied by both chemists and chemical engineers.[1] Also, there are well-known free radical reactions such as halogenation and autoxidation, which serve to functionalize alkanes.[2a-c] These reactions, however, are very non-selective, and are thus limited in their usefulness.

One of the major goals in the chemical world today is to accomplish C-H activation with higher selectivity. This has been one of the main incentives to organometallic research in this area, since homogeneous transition metal systems are known to increase selectivity in many organic reactions. Consequently, the selective activation of carbon-hydrogen bonds under homogeneous conditions using transition metal complexes was sought. Only in recent years have a few examples of such C-H bond activation, especially in alkanes, been reported. These involve, for the most part, stoichiometric rather than catalytic reactions.[3] The ideal goal is to create an efficient catalytic system by which simple alkanes, including methane, can be activated and functionalized.

This paper will begin with the proposal of three ideal catalytic schemes for the activation and functionalization of alkanes using transition metal complexes, followed by a discussion of the mechanisms and various examples of each step in the cycle known to date. The problems of functionalization will be discussed and, finally, specific stoichiometric and catalytic cycles which have been discovered will be shown.

PROPOSED CATALYTIC CYCLES

The ideal situation in selectively activating and functionalizing alkanes would be to utilize a transition metal catalyst. In this way, for example, methane gas could be passed over a catalyst, and with the addition of another reagent, readily activated. Such a functionalization process could

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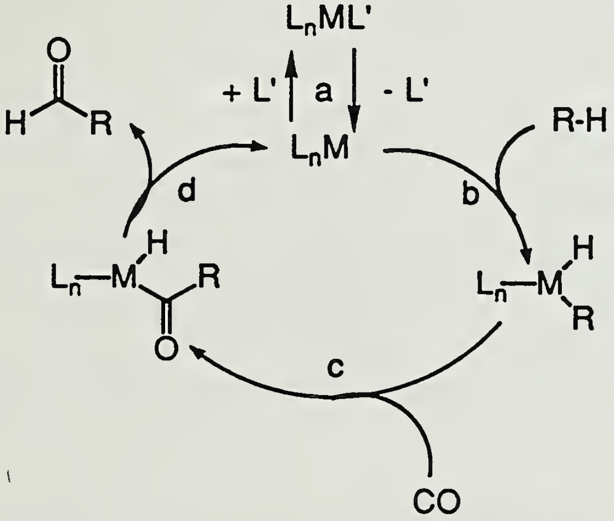
be visualized as taking place by either one of the three catalytic cycles shown in Scheme I, proposed by both Ziegler[4] and Tanaka,[5] Scheme II, proposed by both Crabtree[6] and Tanaka,[7] or Scheme III. These three systems differ mainly in their functionalization steps. They all depend on the oxidative addition of an alkane C-H bond (step b). The intermediate alkyl can then be trapped in a number of ways depending on the reaction conditions and the particular metal involved (step c). The terminal step yields the activated product by reductive elimination, regenerating the catalyst (step d). In the first cycle (Scheme I), the alkyl decomposes to give an aldehyde after CO insertion, in the second cycle (Scheme II) to give a free alkene by β-elimination, and in the third cycle (Scheme III) to give an alkyl halide. Each of these cycles will be covered in detail with specific examples.

First Catalytic Cycle

The individual steps of the cycle given in Scheme I are as follows: First, a ligand L' is lost, either thermally or photochemically, from the metal complex L_nML' to give the unsaturated intermediate L_nM as the active catalyst (step a). Second, RH, where R is a saturated alkyl group, is oxidatively added to the catalyst through a C-H bond to give the coordinately saturated complex $L_nM(H)(R)$ (step b). Third, the addition of CO occurs to produce the insertion product $L_nM(OCH)(R)$ (step c). Fourth, the reductive elimination of H-CO-R generates the catalyst again (step d).

Scheme I



A necessity for the success of this catalytic cycle, as well as the other two cycles, is the formation of a coordinately unsaturated metal center. In other words, a saturated 18-electron metal complex must be oxidized to a 16-electron metal species in order for addition to the metal center to occur. Generation of the coordinately unsaturated catalyst L_nM has recently been accomplished by photolytic expulsion of CO, PR_3 and H_2 where M is iridium, rhenium or rhodium.[8] None of these coordinately unsaturated species has been isolated to date. One study done by Bergman et.al., however, has actually detected the C-H activating transient intermediate formed from $Cp^*Rh(CO)_2$ ($Cp^* = \eta^5$-C_5Me_5) upon UV irradiation using a novel combination of low-temperature and IR laser flash kinetic techniques.[9] It is assumed, based on extensive precedent,[10] that irradiation of the trimethylphosphine dihydride complexes leads to an electronically excited state which rapidly loses H_2, forming coordinately unsaturated complexes as transient intermediates. Also, irradiation of 18-electron complexes is known to expel donor ligands.

After the unsaturated catalyst is formed, the next step in the catalytic cycle is the oxidative addition of RH forming an 18-electron saturated metal complex. The addition process is formally a two electron oxidation of the metal and removes two electrons from the d-orbitals. The mechanism by which C-H bonds are believed to undergo oxidative addition involves a two electron, three-center transition state. In the transition state, there is donation of electron density from the C-H σ-bond into an empty orbital of σ symmetry on the metal, and π-back-donation of electron density from a filled metal orbital of π symmetry into the C-H σ*-orbital.[11] Like that found for the oxidative addition of H_2,[12] the kinetic isotope effect for the oxidative addition of alkane C-H bonds has been found to be very small, thus suggesting an early transition state for the C-H bond addition to L_nM. For example, the kinetic isotope effect for the reaction of $Cp^*Ir(PMe_3)H_2$ with cyclohexane is 1.38.[8a] Evidence pertinent to the structure of the transition state has been provided by Brookhart and others by the isolation of complexes containing M-H-C agostic interactions.[13] These complexes can be isolated, unlike those in the present study, because they lack a filled π-type orbital of the correct symmetry to back-donate into the C-H σ*-orbital.

In 1982, fragments sufficiently reactive to attack solvent alkane C-H bonds and give a stable alkyl hydride product were geberated by three groups by two different but related methods. The first of these reports was by Bergman,[8a,b,14] who showed that photolysis of $Cp^*Ir(PMe_3)H_2$ in a wide variety of alkanes gives the corresponding alkyl hydride adducts with extrusion of H_2. The highly reactive unsaturated species, $[Cp^*Ir(PMe_3)]$, oxidatively adds cyclohexane, neopentane, cyclopropane, n-pentane and n-propane to give the corresponding hydridoalkyliridium(III) complex, $Cp^*Ir(PMe_3)(R)(H)$. Bergman also observes methane activation by heating the hydridocyclohexyl iridium(III) complex in cyclo-octane in a sealed Pyrex vessel under 20 atm of CH_4 at temperatures between 140-150 °C.[14] Analogously, Feher and Bergman have found the $Cp^*Rh(PMe_3)H_2$ complex to oxidatively add a variety of alkanes after photoextrusion of H_2,[8e,15] while Graham has observed alkane insertion by the $Cp^*Ir(CO)_2$ compound after photoexpulsion of a CO ligand.[8c,d] Graham has also found an efficient and selective carbon-hydrogen activation process by a tris(pyrazolyl)borate rhodium complex.[16] Recently, Bergman has discovered three isoelectronic rhenium(I) complexes that readily add primary alkanes, but not secondary alkanes.[8f,17] Thus, secondary alkanes, such as cyclohexane, can be used as inert solvents, providing a convenient method for activating gaseous substrates such as methane.

The next step of the cycle involves the insertion of CO. The first step of this reaction involves the binding of CO to the metal. In order for the CO to bind to the metal, a ligand must dissociate from an 18-electron metal complex to create a 16-electron, coordinately unsaturated metal center. The dative bonding of the CO to the metal involves the donation of the lone pair on the CO in a σ-type orbital into an empty orbital on the metal of σ-symmetry, and π-back-donation by a filled metal orbital of π-symmetry into the π^*-orbital on the CO. Once the CO is bound, the *cis*-alkyl group then migrates to the coordinated CO through a three-centered transition state, where the M-R σ-bond donates into the π^*-orbital of the CO ligand. Once the migration has taken place, the dissociated ligand recoordinates to the metal.

Examples of alkyl to acyl insertions are known for all of the transition metals.[18] One well studied example involves the pentacarbonylmethylmanganese(I) complex, $Mn(CO)_5Me$. Using ^{14}C-labeled CO, Calderazzo showed that the CO insertion process is intramolecular and that the incoming CO is added *cis* to the acyl group.[18b,19] Migration of the alkyl group has also been found to proceed with retention of configuration.[20]

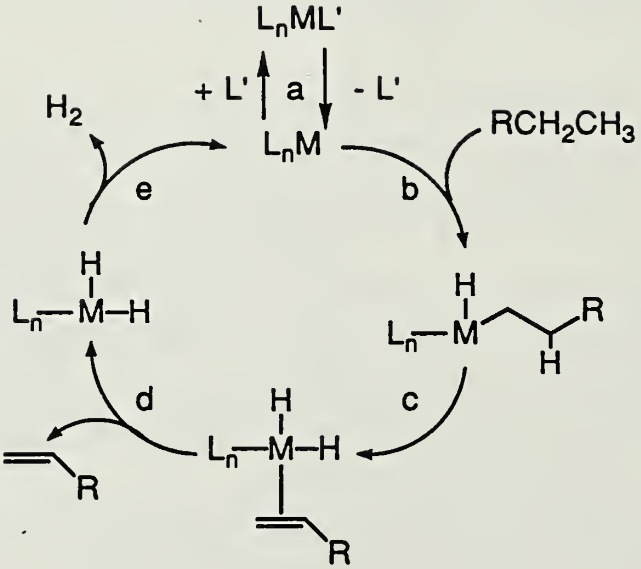
The terminal step in the catalytic cycle is reductive elimination, a bond formation reaction. The mechanism of this process is simply the reverse of that for oxidative addition. It involves the reorganization of orbitals to give a σ-bond between the two dissociating ligands and an empty σ-type orbital and filled π-type orbital on the metal. The metal center is formally reduced to an coordinately unsaturated species.

Many well-known examples of reductive elimination exist.[15b,21] Two specific examples involve the rhodium(III) complex, $L_3RhCl(H)(COR)$, and the platinum(II) compound, $(PPh_3)_2Pt(H)(Me)$. The elimination of aldehyde from the rhodium(III) complex requires initial loss of ligand.[22] The reductive elimination of methane from the four-coordinate platinum complex is so facile that it does not require prior ligand dissociation.[23] The coordinately unsaturated 14-electron complex is then rapidly trapped by diphenylacetylene to give the more stable 16-electron species, $(PPh_3)_2Pt(PhCCPh)$.

Second Catalytic Cycle

The individual steps of the cycle given in Scheme II are as follows: First, a ligand L' is lost, either thermally or photochemically, from the metal complex L_nML' to give the unsaturated intermediate L_nM as the active catalyst (step a). Second, RH is oxidatively added to the catalyst to give the coordinately saturated complex, $L_nM(H)(R)$ (step b). Third, the alkyl ligand undergoes β-hydride elimination to give the dihydride, $L_nMH_2(CH_2{=}CHR)$ (step c). Fourth, the alkene is released, generating the coordinately saturated dihydrido species, L_nMH_2 (step d). The cycle is then continued by the photoextrusion of H_2.

Scheme II



The coordinately unsaturated intermediate is formed as previously stated (step a). Then once again the reactive metal species undergoes oxidative addition of RH to form the saturated hydridoalkyl metal complex. The alkyl compound, RH, in this case must contain a β-hydrogen. The next step (step c) is the functionalization step whereby the hydridoalkyl complex decomposes by β-hydride elimination. The mechanism for this particular elimination can be viewed as occuring through either a four-center transition state or a three-centered transition state. Each transition state leads to the corresponding resonance structure of the intermediate, either an olefin bound metal complex or a metallocycle, to yield the free alkene. In order for the alkyl to eliminate, the alkylhydrido complexes must be coordinately unsaturated, with available *cis* coordination sites. This requirement explains the kinetic stability of transition-metal alkyls which are coordinatively saturated by tightly bound ligands, and of alkyls for which vacant *cis* coordination sites are not available. Also, sterically congested metal alkyl centers do not undergo elimination.

As stated, the next step in the cycle is the loss of the alkene (step d), yielding the metal dihydride complex. This process is usually aided in the addition of an originally dissociated ligand to give the coordinately unsaturated species needed for β-elimination to occur (step c).

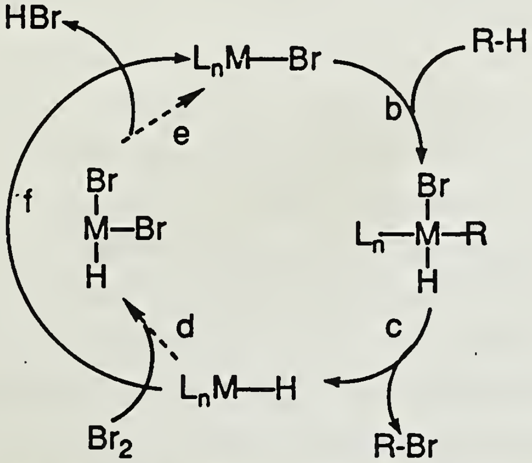
Many examples of β-hydride elimination exist, mainly because the process is so facile.[24,25] It is one of the leading decomposition pathways for many metal-alkyl complexes. A well-known example of this process, studied by Whitesides,[26] utilizes the $(PPh_3)_2Pt(C_4H_9)_2$ complex. In order for the platinum(II) complex to undergo elimination, one of the phosphine ligands must be lost to produce the orbitals of the correct symmetry to be used in the β-hydride elimination. Reductive elimination of both the hydride produced in the hydride elimination reaction and the second alkyl group also occurs, thus, giving rise to the free alkane.

The last step of the catalytic scheme is the photoextrusion of H_2 to yield the coordinately unsaturated metal species (step e). This step is very common as stated previously.

Third Catalytic Cycle

The third cycle simply involves the repeated sequence of oxidative addition/reductive elimination. There are no known examples of the oxidative addition of RH to metal halide complexes (step b), but, as stated earlier, several examples are known where RH oxidatively adds to such reactive species as [Cp*ML] (Cp* = C_5Me_5, M = Ir, Rh).

Scheme III



Since both bromine and the pentamethlcyclopentane are formally -1 ligands, the oxidative addition of RH to the analogous bromine complexes, such as, [BrML] should be possible.

The second step of the cycle, involving the reductive elimination of an alkyl halide, RX, is a very common process (step c).[27] Heck has shown that the 18-electron compound formed upon the addition of methyl iodide to Vaska's complex readily reductively eliminates the methyl iodide upon heating.[28]

The last two steps of the cycle (steps d and e) involve the addition of halide and elimination of HX. Although the two individual steps have not been observed as discrete reactions, the overall reaction (step f) has much precedent.[29] The mechanism of this reaction has been the subject of much study and is as yet unknown. It is thought to possibly involve a four-center transition state between the metal, carbon and two bromine atoms. Steps d and e would be the favored pathway if they could be made to occur.

This cycle presents a third way of attempting to activate simple alkanes due to the precedents of each step.

PROBLEMS IN FUNCTIONALIZING THE HYDRIDOALKYL COMPLEXES

Many examples are now known for the C-H activation of alkanes by soluble transition-metal complexes. Ways of successfully oxidatively adding C-H bonds, once thought to be very difficult, are now well established. Unfortunately, however, completion of the actual functionalization of alkanes has been frustrated in most systems by the reverse reaction of oxidative addition. That is, the rate of reductive elimination of RH to regenerate alkane is often substantially greater that that of the functionalization step. A typical example of this is in the attempt to functionalize an alkane after it has been added to a metal by CO insertion.[30] This is due to the type of bonding involved between the CO ligand and the metal, as explained earlier. The more electron density on the metal, the more tightly CO binds to a metal center due to the π-back-donation from the metal. As the CO ligand binds to the metal in a hydridoalkyl complex, it induces the reductive elimination of the alkane in order to produce more electron density on the metal for which it can use in back-donation to the CO ligand. Most of the attempts to cause a hydridoalkyl metal complex to undergo CO insertion have failed because of this competition for electron density on the metal by the CO ligand. The addition of other reagents, such as Br_2 and H_2O_2, have also been found to simply cause the reductive elimination of the added alkanes.[10b]

Both Bergman[30] and Merola[31] have developed separate systems which have blocked the the nonproductive back-elimination pathway. Bergman uses an (η^3-allyl)(hydrido)iridium(III) complex to trap the hydride after the oxidative addition of RH, while Merola uses an iridium chloride complex to functionalize the hydride ligand.

A second problem in the activation of alkanes is the fact that many of the hydridoalkyl complexes are not stable at room temperatures. Therefore, they can be formed, but upon warming they decompose, either by way of β-hydride elimination or reductive elimination.

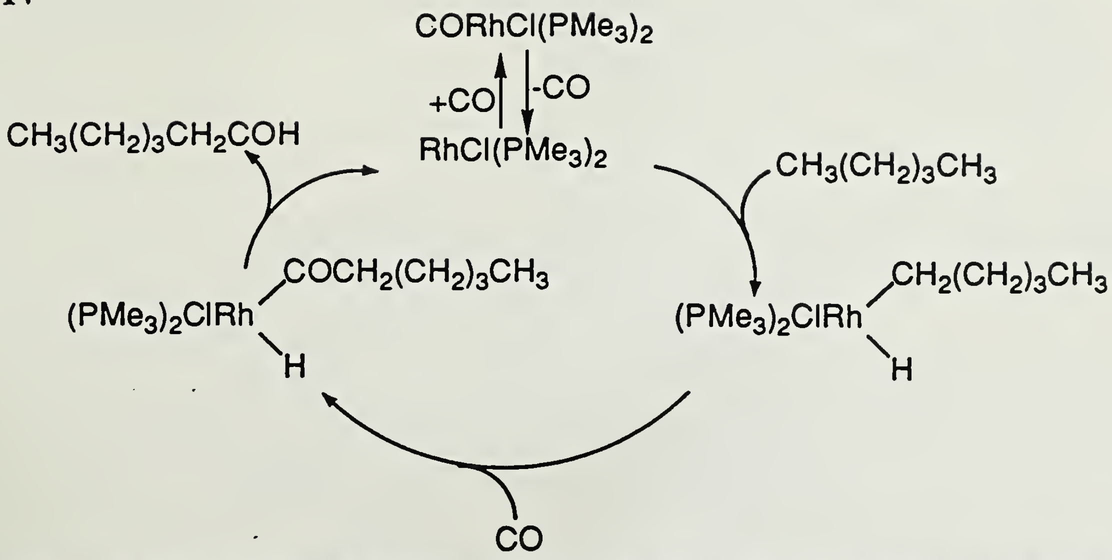
Studies are being carried out in attempt to continue the chain of reactions needed to successfully functionalize alkanes.

STATE OF THE ART TODAY IN TERMS OF PROGRESS

In only a few systems has the product of the insertion been converted, either stoichiometrically or catalytically, into functionalized products. This once again is due to either the instability of the hydridoalkyl complex at certain temperatures or the inability to add other ligands to the metal center without promoting reductive elimination.

Recently, three catalytic systems have been developed in which simple alkanes have successfully been functionalized. Tanaka has developed a catalytic system in which alkanes are converted to their corresponding aldehydes.[32] The proposed mechanism for this process is as shown in Scheme IV. He shows that the catalytic carbonylation of alkanes is highly regioselective toward primary C-H bonds. The number of turnovers is poor (28 for pentane), however, due to relatively rapid decomposition of the catalyst.

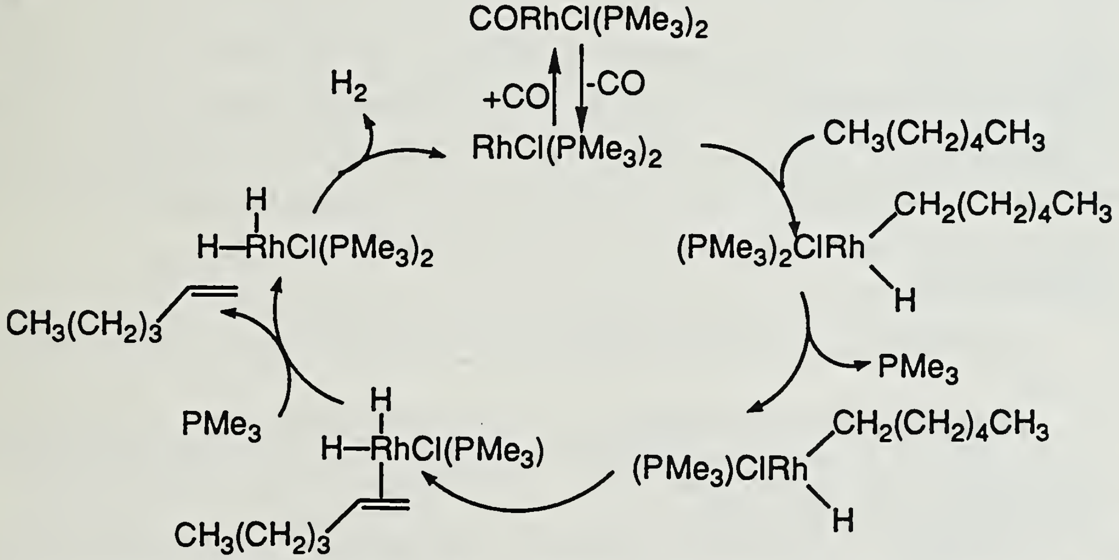
Scheme IV



Tanaka has also utilized the same rhodium catalyst in the conversion of alkanes to alkenes.[33] The proposed mechanism is as shown in Scheme V. This system has no need for a hydrogen acceptor and it shows high catalytic activity (195 turnovers).

A second catalytic system has been developed for the dehydrogenation of alkanes by Crabtree.[34] The mechanism which has been proposed for this process is given in Scheme VI. The reaction has been found to be the most successful with cyclo-octane. The acetate group in this species is known to open and close easily which is important in the β-hydride elimination step of the cycle.

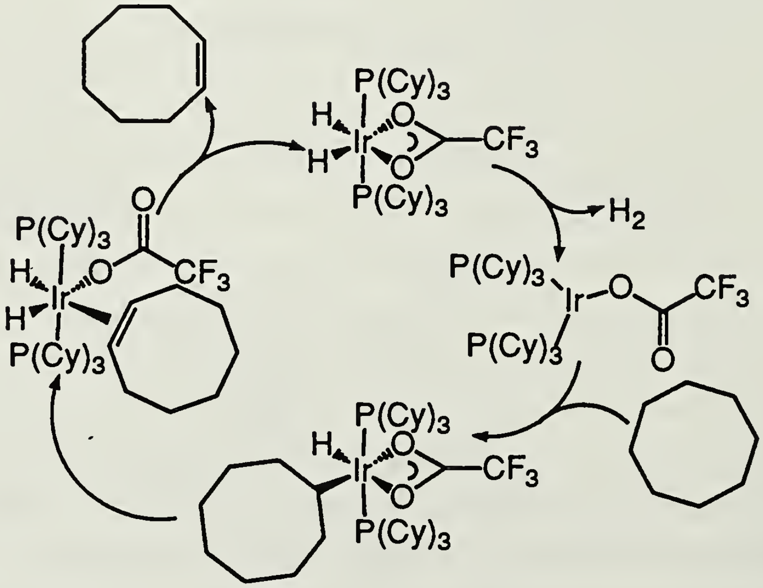
Scheme V



No catalytic system has yet been developed for the formation of alkyl halides. Bergman,[10a,b,16a] however, has developed stoichiometric processes which form alkyl halides.

These systems involve radical mechanisms following the oxidative addition of alkane and thus, are not as useful.

Scheme VI



CONCLUSION

The activation of alkanes has progressed rapidly in the last several years, but general approaches with widespread applicability are still lacking. As shown, a few catalytic systems have been developed for both the carbonylation and dehydrogenation of alkanes, which are proposed to occur via the cycles in Schemes I and II, respectively. These systems are far from being extremely efficient, yet they clearly demonstrate that such processes of alkane activation are possible. No catalytic system has been developed to convert alkanes into alkyl halides. The catalytic cycle given in Scheme III, therefore, is potentially such a process. In conclusion, intermolecular homogeneous activation of alkane C-H bonds by transition metal complexes may prove to be the method of choice in obtaining the high selectivity that is desired.

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ANALYSIS OF DNA SEQUENCE SPECIFICITY OF LEXITROPSINS

Reported by Monica B. Lamb March 1, 1990

INTRODUCTION

Lexitropsins are DNA groove binding oligopeptides based on the naturally occurring antiviral and antibiotic agent, netropsin (Figure 1).[1,2,3] Netropsin is known to specifically bind in the minor groove of B-DNA to a deoxyadenosine (dA) and deoxythymidine (dT) sequence (5'-AATT-3') and to act as an inhibitor of replication and transcription.[4] DNA sequence specific drugs could be useful as gene control agents or as models in understanding the sequence specific molecular interactions between DNA and proteins. Hydrogen bonding, van der Waals contacts, and electrostatic interactions are important in the complexation of netropsin to double-stranded B-DNA, and it is these interactions which are believed to influence sequence specificity.[1,2,3] Lexitropsins have been studied ina an effort to understand these interactions and particularly to develop deoxyguanosine (dG) and deoxycytodine (dC) sequence specificity.

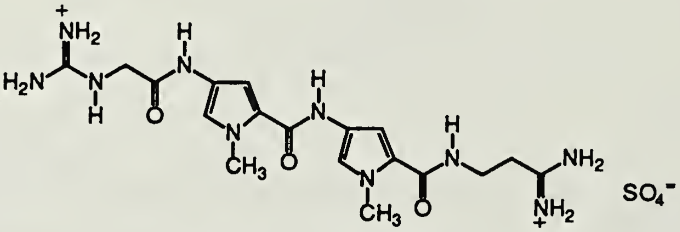

Figure 1. Netropsin.

DESIGN AND SPECTROSCOPIC STUDIES OF LEXITROPSINS

Insight into the design of lexitropsins requires an understanding of the important interactions found for the netropsin/DNA complex. An X-ray crystal structure of netropsin complexed to a double-helical B-DNA dodecamer of sequence CGCGAATT-^{Br}CGCG has been reported revealing a number of important structural features and interactions for the complex.[2] In the crystal structure, netropsin is a bow-shaped molecule with its hydrogen donating amide groups (NH) located on the concave face (Figure 2). The N-4, N-6, and N-8 amide hydrogens form bifurcated hydrogen bonds with the dA·dT sequence.

From the X-ray analysis, it was postulated that netropsin could not bind to (dG)·(dC) sequences due to the steric hindrance caused by the C-2 amine group on dG. Thus, it was argued that the actual sequence specificity was due to favorable van der Waals contacts between the C-2

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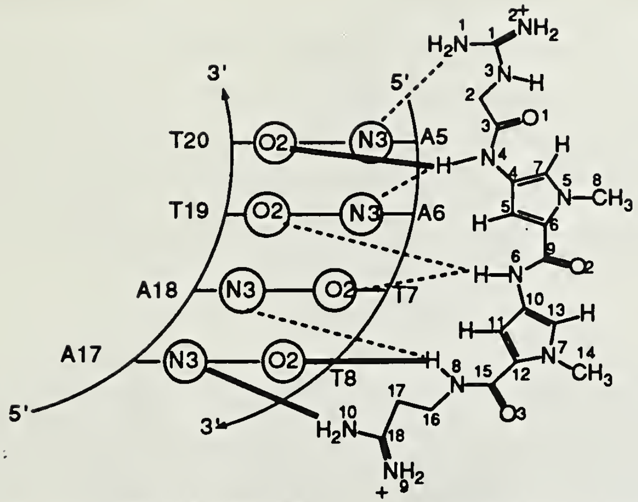


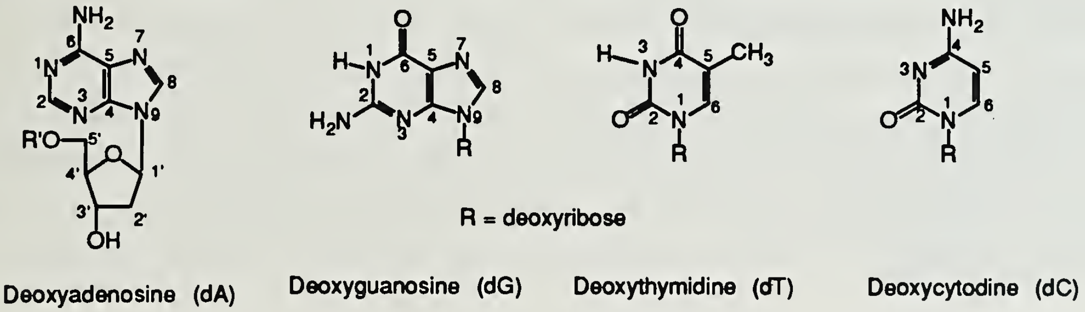
Figure 2. Interactions between netropsin and a d-(A·T)$_4$ sequence. Bold lines indicate distances short enough for standard hydrogen bonds, and dotted lines indicate distances of 3.2 Å or more.[2a]

atoms of each dA and the C-2, C-5, C-11, and C-16 atoms of netropsin. The values listed in Table I contrast the distances of the C-2, C-5, C-11, and C-16 atoms of netropsin and the C-2 atoms of each dA with the distances calculated for a hypothetical case involving dG C-2 amine groups (see Scheme I for numbering system). The distance between the netropsin atoms and the C-2 atoms of each dA indicates close van der Waals contacts. Addition of an amine group at C-2 of dA (i.e. C-2 amine of dG) will shorten the distance to the netropsin atoms so that favorable van der Waals interactions are no longer possible. Thus, no preference for binding to dG·dC regions in DNA is found, and netropsin "reads" dA·dT sequences instead.

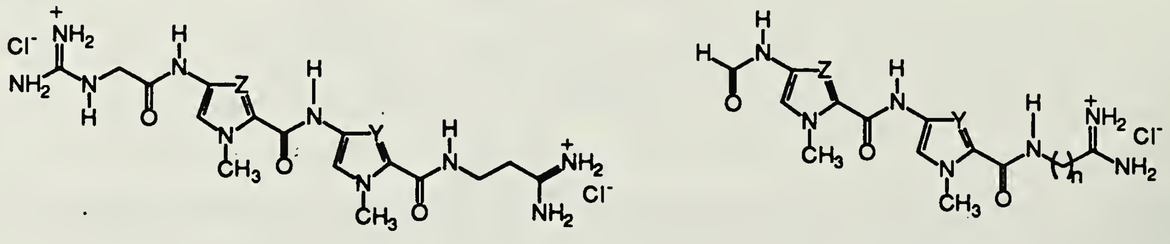
Table I. Distance from netropsin atoms to dA or dG bases of DNA in the minor groove.[2a]

Netropsin Atom	C-2 of dA	Distance for dA	C-2 amine of dG	Distance for dG
C-2	A-5	3.90 Å	G-5	3.05 Å
C-5	A-6	4.06 Å	G-6	3.11 Å
C-11	A-18	3.87 Å	G-18	2.87 Å
C-16	A-17	3.94 Å	G-17	2.92 Å

Scheme I



Since the distances calculated in Table I for the atoms of netropsin and the C-2 amine group of each dG seemed ideal for hydrogen bonding, C-5 and C-11 on the pyrrole rings of netropsin could be replaced with a hydrogen bond acceptor. Exchanging the pyrrole units with imidazole units might allow hydrogen bonding to occur between the imidazole-N and the C-2 amine of dG. Lexitropsins **1-3** (Figure 3) were synthesized with each containing one or two imidazole units.[5] Of the three analogues, lexitropsin **3** was studied extensively and revealed the most interesting results.



1 Y = CH, Z = N
2 Y = N, Z = CH
3 Y = Z = N

4 Y = Z = CH, n = 2
5 Y = CH, Z = N, n = 2
6 Y = N, Z = CH, n = 2
7 Y = Z = N, n = 2
8 Y = Z = CH, n = 1

Figure 3. Lexitropsins **1-8.**

DNA footprinting studies were performed between **3** and a 139 base pair *Hind*III/*Nci*I restriction fragment of pBR322 DNA end-labelled with (α-^{32}P) dATP.[6] At a drug-to-DNA base pair ratio (r_t) of $0 < r_t < \sim 0.17$, compound **3** inhibits enzymatic cleavage of the phosphodiester bonds of DNA at regions 50-45 d-(ATAAAC), 62-56 d-(AATTTAA), and 94-85 d-(AGATTTCATA) similarly to netropsin. As the r_t is increased, $\sim 0.17 < r_t < \sim 0.5$, dG·dC rich areas are inhibited. At high r_t (>5), compound **3** is found to inhibit at almost every nucleotide. The change in the melting temperature of DNA (ΔT_m) for **3** with calf thymus DNA at a drug/phosphate ratio of 0.25:1 is 12° compared to 21.5° for netropsin. The binding constant of lexitropsin **3** determined by ethidium bromide displacement[7] using calf thymus DNA is 1.76×10^6 M^{-1} which is strong but decreased from that of netropsin which has a value of 1.87×10^6 M^{-1}.

Structural aspects and binding specificity of **3** to a B-form decadeoxynucleotide, d-$(CGCAATTGCG)_2$, were determined using 1- and 2-D ^1H NMR techniques.[8] The ^1H-NMR spectrum reveals that the most observable changes in chemical shifts are for the sequence A_4-T_7 (Scheme II). A more definite indication of binding to this site is shown by the chemical shift changes of the Watson-Crick hydrogen bonding exchangeable protons (imino protons) IV and V. These results are summarized in Table II. These experiments give conclusive results that **3** is bound along the 5'-AATT-3' sequence in the minor groove. Although DNA footprinting studies revealed that 3 can bind to dG·dC sites, the NMR evaluation clearly shows a strong preference for the 5'-AATT-3' site.

Scheme II

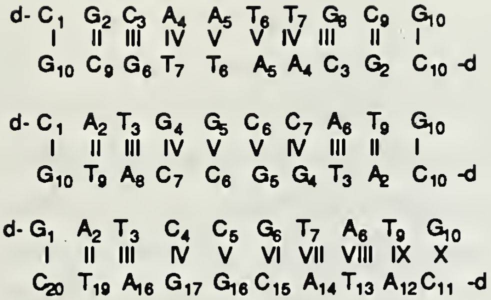

d- C1 G2 C3 A4 A5 T6 T7 G8 C9 G10
I II III IV V V IV III II I
G10 C9 G8 T7 T6 A5 A4 C3 G2 C10 -d
d- C1 A2 T3 G4 G5 C6 C7 A8 T9 G10
I II III IV V V IV III II I
G10 T9 A8 C7 C6 G5 G4 T3 A2 C10 -d
d- G1 A2 T3 C4 C5 G6 T7 A8 T9 G10
I II III IV V VI VII VIII IX X
C20 T19 A18 G17 G16 C15 A14 T13 A12 C11 -d

Table II. ^{1}H NMR Chemical shifts (in ppm) of base and imino protons in free and complexed DNA with lexitropsin **3** at 21 °C in D_2O solution.[8]

Proton	DNA	1:1 Complex	Chemical Shift Change
A_4H8	8.26	8.29	0.04
A_5H8	8.19	8.20	0.01
T_6H6	7.13	7.04	-0.05
T_7H6	7.28	7.09	-0.18
IV	13.72	14.01	0.29
V	13.58	13.79	0.22

A theoretical study on the electrostatic interactions of netropsin with B-DNA was the foundation for additional structural changes of netropsin.[3] It was found that the electrostatic interactions between the dicationic netropsin molecule and the negative well potential in the minor groove of the DNA in the 5'-AATT-3' base pair region played an important role in sequence specificity. Pullman[9a] calculated the electrostatic potentials of B-DNA using 22 nucleotide sequences of $(dA)_{11}\cdot(dT)_{11}$ and $(dG)_{11}\cdot(dC)_{11}$ *in vacuo* and in water. Calculations of electrostatic potentials in both the gas and aqueous phase indicate that the dA·dT region in the minor groove is more negative than the dG·dC region. It was reasoned that the negative potential was located along the middle of the minor groove instead of being associated with the negatively charged phosphate backbone of DNA. The strong negative potential attracts the dicationic drug and controls the specificity. If this were the case, reducing the cationic charge from +2 to +1 should decrease dA·dT sequence specificity. Furthermore, the addition of imidazole units should enhance dG·dC sequence specificity. Lexitropsins **4-7** were synthesized with an *N*-formyl group replacing the cationic guanidinium group of netropsin.[10,11] Compound **7** was studied most extensively due to its monocationic *bis*(imidazole) structural feature.

DNA footprinting experiments with **7** were performed identically to that for compound **3**.[11] Compound **7** is found to inhibit strongly at an $r_t = 0.06$ at only two sites, 85-76 and ~127 to ~119, having essentially the same sequence of 5'-(C or G)ACGGTGCC-3' specifically along the 5'-CCGT-3' (or 5'-ACGG-3') site. The binding constant arrived at by ethidium bromide displacement[7] using calf thymus DNA is $4.91 \times 10^5 M^{-1}$ as opposed to $1.87 \times 10^6 M^{-1}$ for netropsin.

As the DNA footprinting results for **7** indicate a preference for binding to dG·dC rich regions, the decadeoxynucleotide d-$(CATGGCCATG)_2$ was used for the NMR studies to confirm this specificity.[12] Proton NMR studies of a 1:1 drug:DNA complex demonstrated a doubling of resonances for C_6H6, C_7H6, A_8H8, T_9H6 (see Scheme I). Since doubling occurs only in this region, the drug is thought to be bound at the 5'-CCAT-3' sequence, a supposition supported by examination of the proton COSY and 1-D NOE difference spectra. Table III summarizes the ^1H NMR results along with the proton chemical shift changes for the free and complexed nucleotide. DNA thermal denaturation studies of **7** with the decadeoxynucleotide gave a ΔT_m of 10° over the free decadeoxynucleotide implying that this compound provides stabilization to the DNA helix.

Table III. ^1H NMR Resonance Assignments (in ppm) of drug 7:DNA Complex 1 at 21 °C in D_2O Solution.

Base	DNA	1:1 Complex	$\Delta\delta$
C_6H6	7.38	7.03, 7.49	0.11, -0.35
C_7H6	7.52	7.45, 7.59*	0.07, -0.07
A_8H8	8.39	8.10, 8.37	-0.02, -0.29
T_9H6	7.17	6.82, 7.13	-0.04, -0.35

*These values were assigned by evaluation of the 1-D NOE difference spectrum.

As a follow-up to the previous study, a ^1H NMR experiment was performed by employing **7** and the decadeoxynucleotide d-[(GATCCGTATG)·(CATACGGATC)].[13] This sequence bears a 5'-CCGT-3' site that is bound strongly by **7** in the DNA footprinting studies. The ^1H NMR spectra of free relative to the complexed nucleotide show a doubling of resonances for the 5'-CCGT-3' site indicating that **7** is bound along this site (Table IV).

Table IV. ^1H NMR Resonance Assignments (in ppm) of drug 7:DNA Complex 2 at 21 °C in D_2O Solution.

Base	DNA	1:1 Complex	$\Delta\delta$
C_4H6	5.55	5.72	0.17
C_4H5	7.55	7.52, 7.64	0.09, -0.03
C_5H6	5.48	5.59	0.11
C_5H5	7.51	7.40, 7.48	-0.03, -0.11
G_6H8	7.68	7.79, 7.81	0.11, 0.13
T_7H6	7.17	6.92, 7.06	-0.11, -0.25

To overcome the van der Waals interactions which prevent the C-16 atom of netropsin from recognizing a dG·dC base pair at the 3' binding site, the "truncated" lexitropsin **8** having only one prochiral methylene group at the C-terminus was examined.[14] Similar to the cases of compounds **3** and **7**, 1- and 2-D ^{1}H NMR experiments were performed using **8** and the decadeoxynucleotide d-(CGCAATTGCG)$_2$. The chemical shifts of the free and complexed DNA (Table V) reveal that **8** is bound from the N- to C- termini along the 5'-ATTG-3' site. These results strongly suggest that the van der Waals contact between the second methylene group and the C-2 amine on dG prevents netropsin from binding to a dG·dC base pair at the 3' binding site. Removal of one methylene group removes the steric interaction, thus **8** can now read the DNA sequence and bind to a dG·dC base pair.

Table V. ^{1}H NMR Resonance Assignments (in ppm) of drug **8**:DNA Complex at 21 °C in D_2O Solution.

Base	DNA	1:1 Complex	Δδ
A_5H8	8.20	8.31	0.11
T_6H6	7.13	6.99	-0.14
T_7H6	7.28	6.99	-0.29
G_8H8	7.88	7.82	-0.06

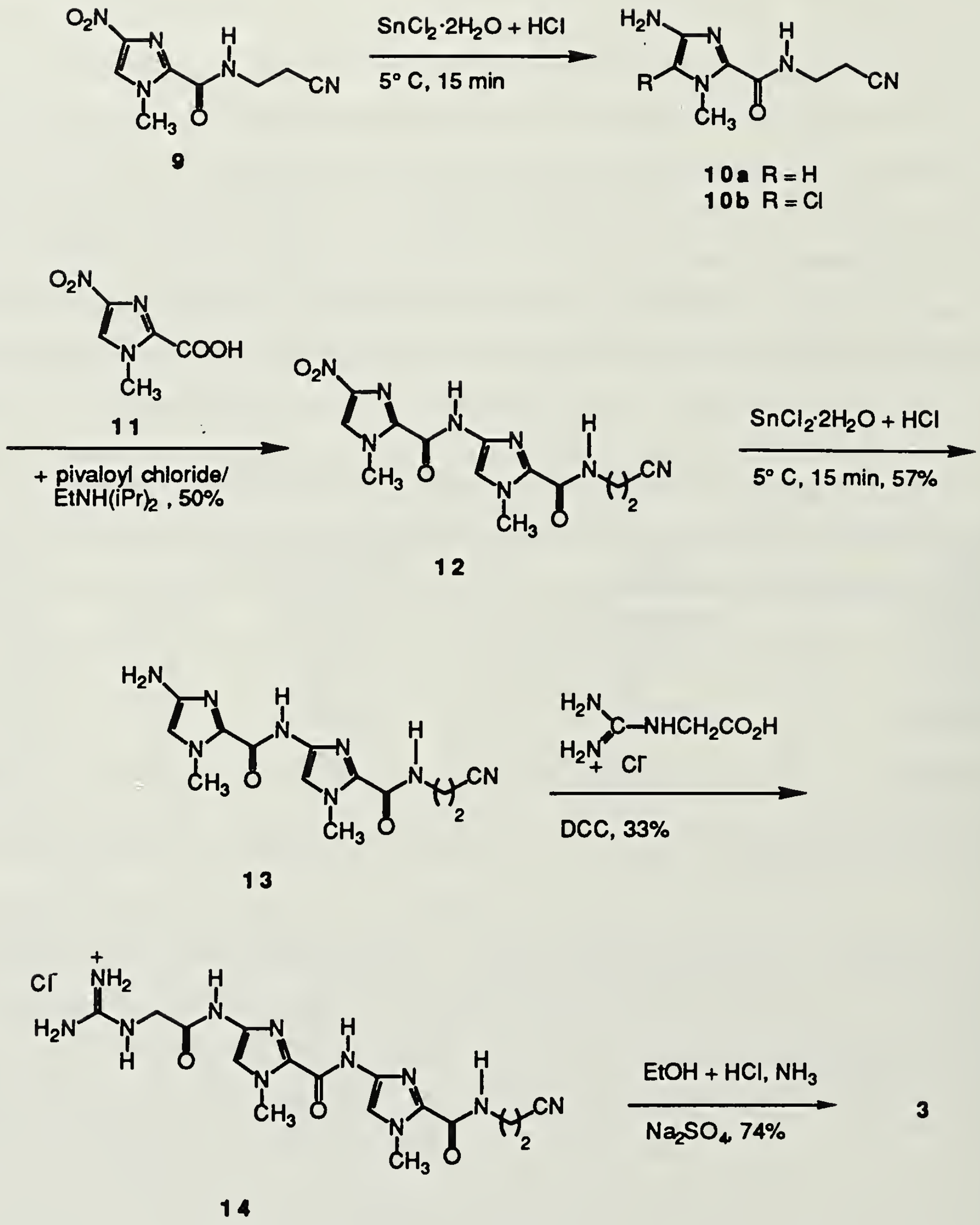
GENERAL SYNTHESIS

Lown and coworkers have reported extensive work on the synthesis and binding of the proposed lexitropsins to double-stranded B-DNA. All lexitropsins studied were synthesized in a similar manner. A detailed synthesis of lexitropsin **3** is presented in Scheme III.[5] Catalytic reduction of the nitro group on imidazole **9** using hydrogen and palladium on carbon is not feasible on large scale. However, an alternative method using stannous chloride was problematic due to the formation of two products, **10a** and **10b**. As **10a** and **10b** were inseparable, the mixture was allowed to react with the mixed anhydride of the carboxylic acid **11** to form **12**. Reduction of the nitro group on **12** under these conditions results in *bis*(imidazole) **13**.

The guanidineacetyl unit was introduced by allowing the free amine of **13** to react with guanidineacetic acid hydrochloride and dicyclohexylcarbodiimide (DCC) in dimethylacetamide (DMA). This method produces low yields (33%) of the desired product; however, alternative routes were unsuccessful. The amidinium group was introduced through the modified Pinner[15] reaction. Addition of anhydrous ethanol saturated with gaseous hydrochloric acid followed by addition of dry ammonia gas to *bis*(imidazole) hydrochloride **14** results in lexitropsin **3**.

Lexitropsins **4-8** were synthesized in the general manner described in Scheme II with the exception of the incorporation of the guanidineacetyl unit.[10,14] The *N*-formyl group was

Scheme III



introduced in place of the guanidinium group by treatment with *N*-formylimidazole forming lexitropsin **8** in an 81% yield. *N*-formylimidazole was formed by the reaction of 98% formic acid with carbonyldiimidazole in methanol or dimethylsulfoxide.

CONCLUSION

Lexitropsins **3**, **7**, and **8** all show, to some extent, an increase in specificity for dG·dC rich sequences. This increase seems to be a result of both van der Waals and electrostatic interactions. Lexitropsin **3**, although binding to a dA·dT sequence in the NMR studies, shows appreciable selectivity for dG·dC regions in the DNA footprinting experiment. Modifying **3** by reducing the cationic charge from +2 to +1, as in lexitropsin **7**, leads to a marked increase in dG·dC sequence selectivity. Finally, the combination of removing a methylene group from the C-terminus of netropsin and reducing the cationic charge to +1, as in lexitropsin **8**, enables the molecule to recognize a dG·dC base pair at the 3' binding site.

Using the knowledge gained from the studies of lexitropsins **3**, **7**, and **8**, three important structural features are required for altering sequence specificity. Incorporating imidazole units into the lexitropsins allows hydrogen bonding between the nitrogens on the ring and the C-2 amine hydrogens on dG. Reducing the cationic charge on the lexitropsins reduces the attraction between the molecules and the negative well potentials in the minor groove of double-stranded B-DNA, thus reducing dA·dT selectivity. Removing a methylene group from the C-terminus of lexitropsins removes the steric interactions of this group with the C-2 amine of dG. Thus the lexitropsin can now bind to a dG·dC base pair at the 3' binding site. An obvious follow-up to these experiments would be to determine the sequence specificity of binding a monocationic, truncated, *bis*(imidazole) lexitropsin to a decadeoxynucleotide with a 5'-CCGG-3' sequence. Also, since DNA footprinting reveals only sequence binding specificity and not the exact nature of binding, a competition experiment involving DNA thermal denaturation techniques using the above model lexitropsin and natural DNA sequences with differing dG·dC compositions could determine the whether the molecule is actually specific for dG·dC versus dA·dT sequences.

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PROXIMITY EFFECTS IN SOME INTRAMOLECULAR SYSTEMS

Reported by Lisa Beattie March 29, 1990

INTRODUCTION

In general, an intramolecular reaction proceeds faster than its intermolecular counterpart. While some researchers insist rate enhancements seen in intramolecular and enzymic systems on the order of 10^6 or higher can be explained in conventional terms, others have introduced new concepts.[1] One of these is Menger's spatiotemporal hypothesis. In 1985 Menger advanced[1c] that the rate of reaction between functionalities A and B is proportional to the time that A and B reside within a critical distance (to be defined for a particular reaction) in the ground state. Others have proposed similar relationships. Koshland proposed in 1970 that the angle of approach of the attacking species was critical to reactivity in his "orbital steering" hypothesis.[2] While it has been recognized that gross changes in angle of attack affect reactivity in some reactions, there has been much opposition to Koshland's proposal.[3] Work is still being done to determine if there is any validity to Menger's hypothesis. Both proposals relate the geometry of the reacting moieties to reactivity; thus, studies may be designed which test both hypotheses.

The spatiotemporal hypothesis specifies a critical distance must be achieved in order for the species to react. This distance will vary depending on the system. Menger proposed that within the critical distance reactivity should be a function of the distance.

In order to keep the time variable constant, studies have been undertaken using intramolecular systems where the reacting moieties are held at small distances in rigid positions. Four such systems are presented. These efforts address the questions of whether the spatiotemporal hypothesis is valid and whether it is necessary or useful in understanding or predicting reactivity.

RECENT THEORETICAL STUDIES ON PROXIMITY EFFECTS

Houk and Dorigo compared theory-based and empirical calculations with experimental results in the case of two reaction types in order to address the validity of Menger's and Koshland's proposals. The two reaction types are the intramolecular hydrogen abstraction by alkoxy radicals and the lactonization of hydroxy acids. The lowest energy ground state conformations for each molecule were determined using Allinger's MM2 force field. Ab initio calculations were performed using the simplest model of each of these reactions to determine the optimum energy and geometry of the transition state of the rate determining step. These results were used to modify Allinger's MM2 force field in order to predict reactivities for individual species.

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Hydrogen Abstraction[4,5]

Ab initio calculations were performed on the gas phase abstraction of a hydrogen atom from methane by a hydroxy radical. The optimum transition state structure had previously been determined by Pople using the 6-31G** basis set and electron correlation energy corrections with second order Møller-Plesset perturbation theory. Houk and Dorigo determined the optimum transition state geometry using the lower level, more economical Hartree-Fock theory and 3-21G basis set. A comparison of the results obtained by the two levels of theory showed some differences, but the C...O distance between the alkoxy radical and the carbon bearing the hydrogen being abstracted remained essentially the same. Thus they repeated these calculations using the lower level of theory while constraining either the C...O distance or the corresponding C-H...O angle to specific values. It was found that as the deviation from the ideal C...O bond length increased the associated activation energy increased, such that a change of 0.3Å resulted in an increase in the energy of activation of 9 kcal/mol, corresponding to a million-fold deceleration. A variation in C...O bond distance of 0.1Å had about as much influence on the energy of the transition state as a variation in angle of approach of 20°.

The resultant geometries from the ab initio calculations were applied to a modified (by the information gained in the ab initio study) MM2 force field to calculate the energies of activation in the gas phase of seven alcohols (shown in Figure 1) capable of forming cyclic ethers via free radical hydrogen abstraction. Houk and Dorigo assume, as have others,[6] that the rate-determining step in the oxidative cyclization of these alcohols by lead tetraacetate is abstraction of a hydrogen atom by the alkoxy radical. Experimental rate data are not available for the cyclizations. Houk and Dorigo compared calculated activation energies to experimental yields[6] with the assumption that the rate of intramolecular hydrogen abstraction versus the rate of background intermolecular reactions is proportional to the yield of cyclic ether. They assume that all side reactions are similar and proceed at similar rates for the seven alcohols. The calculated transition state C...0 bond distances and energies of activation and the experimental yields are presented in Table I. Not surprisingly, the pertinent distance calculated for the transition structure varied little throughout the series. Houk and Dorigo concluded that there was not a correlation between the distance of the reacting species in the ground state (alkoxy radical) and the reactivity as measured by yield. However they did see a correlation between calculated energy of activation and experimental yield.

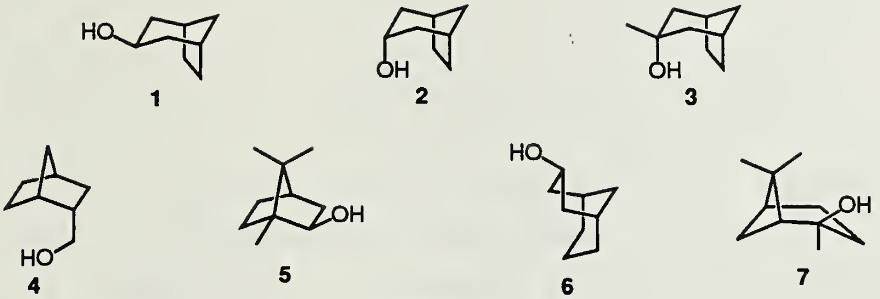


Figure 1

Table I. Comparison of Experimental and Calculated Data For Compounds 1 - 7

	Calculated			Exptl.
Alcohol	ΔE^a, kcal/mol	r (C...O) radical, Å	r(C...O) TS Å	%yield
1	10.8	4.17	2.40	0
2	5.4	3.05	2.44	31
3	5.0	3.03	2.43	61
4	3.8	4.42	2.44	38
5[b]	2.9	3.07	2.44	0
6	1.1[c]	4.59	2.45	86
7	-0.1	2.96	2.43	90

a) $E_{TS} - E_{GS}$ b) Alcohol undergoes β-scission. c) ΔE is calculated to be -1.7 kcal/mol for **6** in the chair-chair conformation, which has a C...O distance of 3.12 Å; 1.1 kcal/mol represents the interconversion barrier between the chair-chair and the more stable chair-boat conformation.

Acid Catalyzed Lactonizations

Houk and Dorigo[4,7] performed ab initio calculations to determine the optimum transition state geometry for the gas phase nucleophilic attack of water on protonated formic acid, which was assumed to be a model for acid catalyzed lactonizations. The results were used to modify the MM2 force field. Energies and geometries were determined for intermediates and transition structures in the acid catalyzed lactonizations of 15 hydroxy acids, including the six bridged bicyclic species shown in Figure 2. The lactonization rates of these compounds were determined spectrophotometrically by Koshland in 1972.[8,9] In this study, the rate determining step was first assumed to be formation of the tetrahedral intermediate. There was little correlation between the calculated and experimental reaction rates. However, there is evidence which indicates the rate determining step for this type of reaction is the collapse of the tetrahedral intermediate.[1d,10] When this case is assumed a good correlation is seen between calculated and experimental reaction rates. Houk and Dorigo found that in the starting materials there was no correlation of the distance between the reacting centers, r(RO...C=O), and relative reaction rate. They saw very little change in r(RO...C=O) of the transition structure throughout the series.

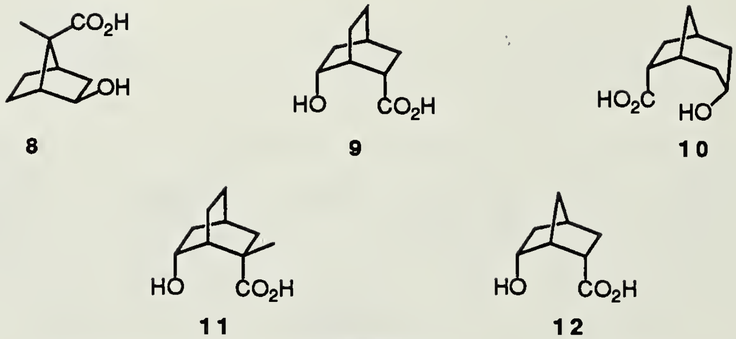


Figure 2

Menger has criticized the method of Houk and Dorigo.[11-13] He claims, among other things, that they did not properly determine optimum ground state conformations. Menger has recently asserted that the transition state modeling technique is not a good predictor of reactivity.[11]

Menger also used MM2 calculations to determine optimum ground state geometries of six bridged bicyclic hydroxyacids including **8** - **12**.[12,13] The optimum C...O distances determined are presented in Table II along with the results of Houk and Dorigo. Menger agrees that there is no correlation of distance between the reacting centers to the experimentally determined rates. He claims this does not disprove his hypothesis, only that other variables, including ring strain, override the distance variable. Houk and Dorigo claim that the Menger model is only applicable to severely limited cases in which the change in strain energy correlates well to the change in the ground state distance between reacting moieties.

Table II. Calculated Geometries and Relative Rates and Experimental Relative Rates For Some Bridged Bicyclic Hydroxy Acids.

	Ground State C...O Distance (Å)		TS‡ C...O	ΔE^a	Rel. Rate
Compound	Houk	Menger	Distance (Å)	(Calcd.)	(Exptl.)
8	2.87	2.88	2.04	12.8	1.0
9	2.98	2.94	2.05	12.7	3.2
10	2.98	2.95	2.05	9.9	33
11	2.84	2.84	2.05	9.9	357
12	2.86	2.87	2.05	9.2	3730

a) Energy of activation, assuming $\varepsilon = 1.5$. ΔE was calculated assuming $\varepsilon = 80$, and the ΔE differences were small and relatively constant throughout the series.

DYOTROPIC HYDROGEN MIGRATION IN *SYN*-SESQUINORBORNENES

Houk suggested that the spatiotemporal hypothesis may be valid in the case where changes in distance between reacting centers are well-correlated with total energy. Paquette's approach to testing the hypothesis involved designing a series of molecules in which the gross structural and electronic features remained constant while the distance between the reacting centers was varied.[14] The structures he chose, a series of *syn*-sesquinorbornenes, were crystalline, thus enabling determination of the ground state distance between reacting centers, at least in the solid state. Compounds **13 - 18** (Figure 3) undergo a thermally allowed dyotropic hydrogen migration when heated, forming the more thermally stable isomer as shown in Scheme I. While the mechanism for this particular series has not been proven, evidence exists for a concerted intramolecular hydrogen migration in a related system.[15] Thus Paquette felt he had designed a system free from as many unaccounted for factors influencing reactivity as possible.

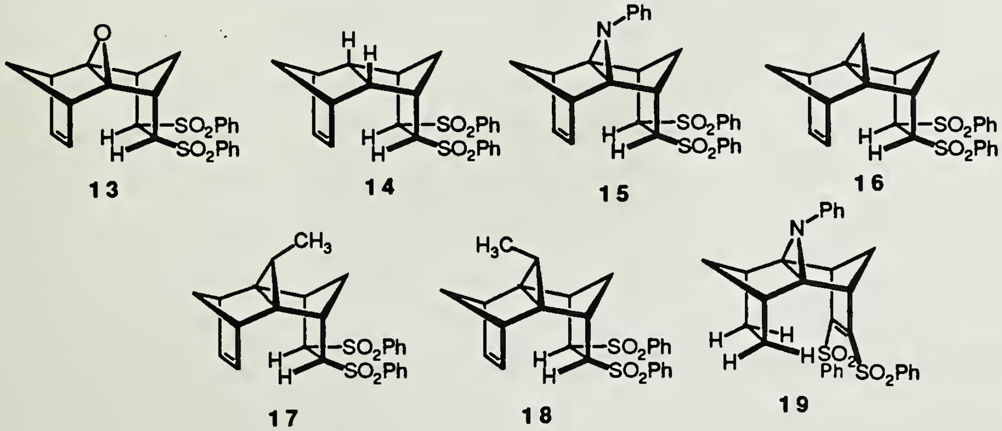
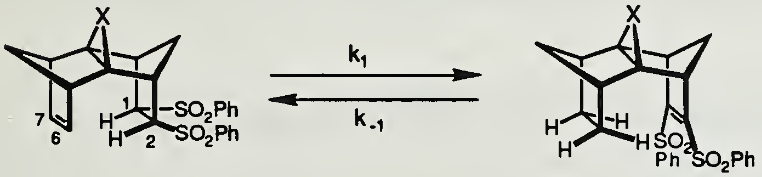


Figure 3

Scheme I



Rate and equilibrium constants were determined for **13 - 18** by measuring disappearance of reactant and appearance of product over time as judged by integration of peaks in the proton NMR spectrum. Distances between reacting centers were determined by X-ray crystal structures of the starting materials. Diastereomers **17** and **18** were inseparable and were determined by proton NMR to be present in a *ca.* 2:1 ratio. Proton COSY and nOe studies proved **17** to be the major isomer. The X-ray crystal structure of the **17/18** mixture was well enough defined in the region of interest to permit distances between reacting centers to be determined. The distance defined was between C(1)-H and C(7) and between C(2)-H and C(6) as shown in Scheme I. Positions of the individual hydrogen atoms were not located but were calculated based on the heavy atom framework. The crystal structures of the disulfones showed deviations from C_s symmetry resulting in differences in the C(1)-H...C(7) and C(2)-H...C(6) distances within each molecule. Paquette used an average distance in making comparisons. The intercavity angles defined by C(1)-H...C(7) and C(2)-H...C(6) were also considered, and were found to range from 117° to 123° in the starting materials. The intercavity distances and relative rate constants are presented in Table III along with data for **19**, the dyotropisomer of **15**, for which a crystal structure was obtained.

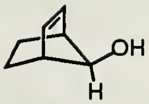
Table III. Relative Rates of Hydrogen Migration and X-Ray Crystal Structure Data for **13 - 19**

	Distances, Å			Relative Rate
Compound	C(1)-H...C(7)	C(2)-H...C(6)	Average	(k_1)
13	2.60	2.46	2.53	1
14	2.44	2.37	2.41	24
15	2.40	2.41	2.40	440
16	2.32	2.31	2.32	4100
17	2.31	2.26	2.28	25200
18	"	"	"	48000
19	2.38	2.39	2.38	-----

The data show that as the distance between the reacting centers decreases the rate increases. A 10^4 rate increase reflects a change in distance of less than 0.3Å. Paquette states that his data are in line with both Menger's and Houk's assertions. He interprets the rate increase as a reflection of the decrease in energy required to stretch the reacting C-H bonds into the proper transition-state geometry.

BIRCH REDUCTION OF OLEFINS WITH PROXIMATE HYDROXY GROUPS

It has been demonstrated that the presence of hydroxy- or carboxy- groups proximate to a double bond can alter the normal regio- and stereochemical outcome seen in the Birch reduction of a variety of substrates.[16] It is believed that the proximate group serves as a proton source or as a template which can bind a proton. It has also been shown that isolated double bonds can be reduced rapidly if a proximate π-donor is present.[17] With this perspective, Paddon-Row and Cotsaris measured the relative rates of the Birch reduction of olefins **20 - 22** as shown in Figure 4.[18] Enhanced rates of reduction were expected due to the OH...π hydrogen bonding interaction and to the presence of a proton which could transfer intramolecularly to the radical anion in what is probably[19] the rate determining step.



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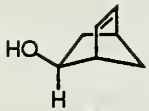

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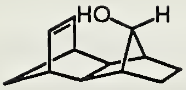

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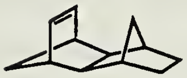

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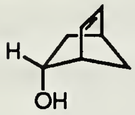

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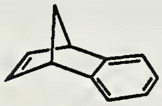
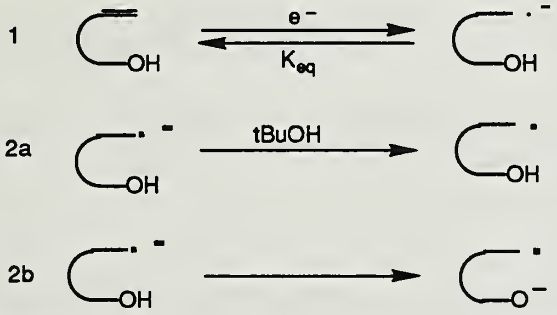


25

Figure 4

Reductions were carried out in an ammonia/tetrahydrofuran solution of lithium. Competition studies were performed in which a second olefin, unable to undergo intramolecular hydrogen bonding or proton transfer, was present in equimolar amounts with the compound of interest. Olefins **23** - **25** were used as competitors, respectively, for compounds **20** - **22**. The olefins competed for a limited amount of lithium in an excess of *t*-butanol. Relative rates were determined based on gas chromatographic product ratios of aliquots quenched as the reduction proceeded. The assumption was made that after the initial one-electron reduction, as shown in Step 1 of Scheme II, the compound containing a hydroxy group proximate to the double bond could undergo proton transfer both inter- and intramolecularly, as illustrated in Step 2, whereas the competitor could only receive a proton from *t*-butanol (2a).

Scheme II



The reductions of substrates **20** and **21** were repeated at various excesses of *t*-butanol to determine both inter- and intramolecular rate constants. The reduction of **22** was so rapid that only complete reduction products were seen. Additionally, the relative first-order rate ratios of **22** to its competitor varied by as much as 25% depending on the mode and rate of mixing. It was assumed that the reaction of **22** proceeded exclusively via intramolecular proton transfer. This assumption was based in part on the observation that compound **21** was reduced faster than compound **20** and also was reduced by intramolecular proton transfer to a greater extent, as evidenced by the rate data.

The relative rates determined in the competition studies were adjusted relative to compound **24** after additional rate studies were completed. This substrate, with a hydroxy group present but unable to participate in hydrogen bonding or intramolecular proton transfer, was thought to be a good model for comparing rate increases due exclusively to the proximity effect.

Paddon-Row and Cotsaris looked for a relationship between the geometry of the OH...π interaction and the rate of reaction. The three geometric parameters used are illustrated in Figure 5.

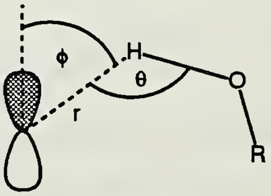


Figure 5

Previous ab initio calculations on the water-ethene complex indicated the strongest OH...π interaction occurs when $\theta = 180°$ and $\phi = 0°$.[20] Approximate values for these parameters for **20** - **22** are presented in Table IV along with the rate data. The STO-3G optimized structure of **20**, a partially optimized STO-3G structure of **21** along with molecular models, and the X-ray crystal structure of the p-nitrobenzoate derivative of **22** were used to determine these parameters. The assumption was made that the anion-radical would have the same geometric requirements as the neutral species. Calculations of the energies and geometries of the radical anion of **20** and of the exo isomer supported this.

Table IV. Polar Coordinates For OH...π Interaction and Rate Data For **20** - **22**

					relative rates[a]	
Compound	r (Å)	θ (°)	φ (°)	%intra-	k_{inter}	k_{intra}
20	2.5	107	20	46	4.43	0.85
21	2.2	121	12	90	17.3	35.1
22	1.8	171	15	100	0	23,000

a) Relative to reduction of **24**, which is assumed to proceed 100% intermolecularly, ±6%.

Based on these results the researchers propose geometric restrictions in order for a substrate to undergo Birch reduction primarily by the intramolecular route. They state that r should be less than 2.2Å, θ greater than *ca.* 110° and φ less than *ca.* 20°. The greater emphasis on distance over angle is in line with Menger's proposal and with the calculations of Dorigo and Houk.

CONCLUSION

Evidence both supporting and disproving Menger's spatiotemporal hypothesis has been found in recent years. The work of Houk and Dorigo indicates that more economical computational methods have been developed to predict reaction rates. Their calculations and Menger's which have been presented do not support the spatiotemporal hypothesis, although Menger has claimed that the effect is not seen because other factors overshadow the distance variable in the systems studied. The dissolving metal reduction of isolated olefins with proximate hydroxy groups illustrates an unusual reactivity explained best by the proximity argument. Paquette's system is unique in that it was specifically designed to test the spatiotemporal hypotheses and in that it does not rely on theory to determine the pertinent distances, although the positions of the hydrogens in the X-ray crystal structures were calculated.

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ASYMMETRIC HYDROSILYLATION OF UNFUNCTIONALIZED KETONES

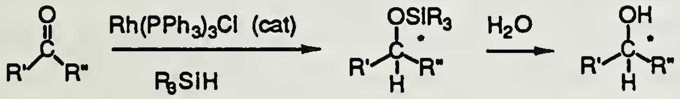
Reported by Lisa Pagh April 5, 1990

INTRODUCTION

Chiral alcohols are important precursors and substrates.[1] One strategy to synthesize chiral alcohols is to enantioselectively reduce ketones, and various methods are available. Chiral boron and aluminum hydrides can be used, but usually only in stoichiometric amounts.[2] However, catalytic chiral boron versions show promise.[3] Asymmetric hydrogenation of ketones can also be used, but yields and enantiomeric excesses (ee's) are not high.[4]

In 1972, Ojima discovered an effective achiral hydrosilylation of ketones to form alcohols (Scheme I).[5,6] Using tris(triphenylphospine)chlororhodium as a catalyst, triethylsilane was added regiospecifically to the carbonyl, with silicon adding to the oxygen and hydride to the carbon. Since the silicon-oxygen bond is easily hydrolyzed, the overall reaction is reduction of the ketone to the alcohol. The reaction conditions were mild, and high yields of the alcohol resulted.

Scheme I



The first report of the enantioselective hydrosilylation of ketones was published in late 1972 by Yamamoto and Kumada.[7] The reaction involved the reduction of acetophenone with $(R_3P^*PtCl_2)_2$, where R_3P^*=(R)-(+)-BMPP **4**, as the source of chirality, and $MeCl_2SiH$ as the silane. The yield was reasonable (81%), but the ee was low (7.6%). Efforts to improve the enantioselectivity have met with moderate success.[8] However, the ee and even the configuration of the product can be very sensitive to the nature of the metal, chiral ligand, silane, and ketone. Analysis of the catalytic cycle and the asymmetric induction step help to explain this sensitivity. Ketones without a functional group near the carbonyl will be considered, as they cannot bind to the metal and are more difficult to reduce by hydrosilylation. Acetophenone is used as a standard.

INFLUENCES ON THE EE AND CONFIGURATION OF THE ALCOHOL

Metal Complex

The most effective and most widely used metal in the asymmetric hydrosilylation of ketones is

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rhodium, because it gives high yields of product and moderate to high enantioselectivity. Kreuzfeld compared rhodium to palladium, iridium, and platinum complexes under the same reaction conditions (Table I).[9]

Table I.Effectiveness of selected noble metals in the asymmetric hydrosilylation of acetophenone[a]

Complex[b]	Time (h)	Yield(%)	%ee	Configuration of product
$[Rh(COD)Cl]_2$	3.5	96.5	51.0	S
$Pd(COD)Cl_2$	7	12.5	50.5	R
$[Ir(COD)Cl]_2$	7	89.5	16.5	R
$Pt(COD)Cl_2$	7	91.0	26.5	R

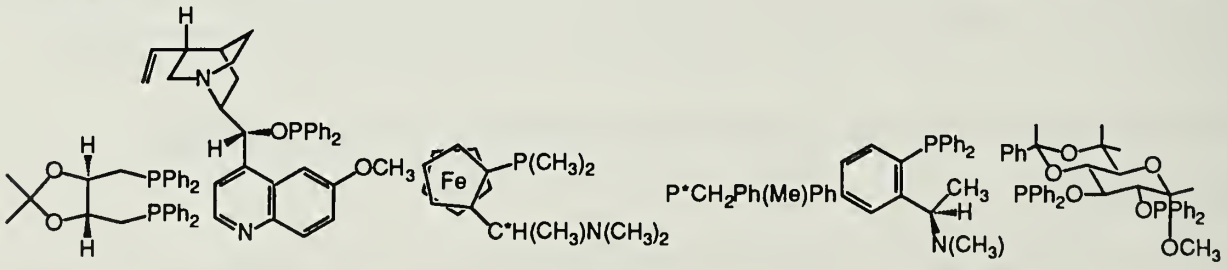
[a] Reaction conditions: chiral ligand is (S)-amphos **5**, metal to ligand ratio is 1:5, Ph_2SiH_2, toluene, 25 °C. [b] COD is cyclooctadiene.

Iridium[10] and platinum[11] give high conversions to the alcohol but lower ee than rhodium, and palladium gives low yield and low ee. The surprising result is the inversion of enantioselectivity due to the change in the metal complex. No explanation is given by Kreuzfeld, but the results clearly indicate a change in catalyst geometry or a change in the mechanism is occuring.

Cationic rhodium BMPP **4** complexes usually form alcohols in lower ee than the neutral complexes.[12,13] A promising result from Brunner showed that metal complexes other than expensive noble metals can be used. Using $Cu(O_2CPh)$ with (–)- BPPFA and H_2SiPh_2 gave quantitative yields of the alcohol, but in low ee (28.9%), favoring the R isomer.[14]

The enantioselectivity of the product is also influenced by the chiral ligand. Initially, the ligands tried were borrowed from asymmetric hydrogenation chemistry, and contained phosphorous atoms which bind to rhodium, as shown in Scheme II. The results of the hyrdrosilylation of acetophenone with rhodium and various hydrosilanes with phosphorous ligands is shown in Table II. Note that the ee is only moderate. Interestingly, bidentate ligands have no advantage over the monodentate ligands.

Scheme II



1 **2** **3** **4** **5** **6**

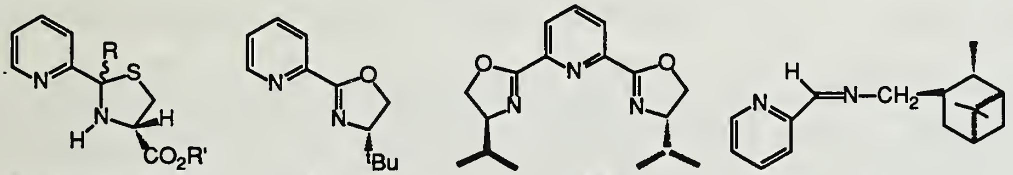
Table II. Hydrosilylation of Acetophenone with $[Rh(COD)Cl]_2$ and various chiral ligands[a]

Ligand	Title	Yield (%)	%ee	Configuration of product
1	(-)-DIOP[15]	100	55	R
2	(8S,9R)-quinine-DPP*[16]	95	50	R
3	(R)-(S)-MPFA[17]	89	49	R
4	(-)-(S)-BMPP[12]	92	44	R
1	(+)-DIOP[18]	100	58	S
2	(8R,9S)-quinidine-DPP*[16]	97	58	S
5	(S)-amphos[9]	96	51	S
6	Glup[19]	98	47	S

[a] Various silanes were used, and reaction conditions were not consistent for each ligand.

Brunner made a conceptual leap by using nitrogen chelating chiral ligands, shown in Scheme III. Much higher ee resulted, while still keeping the high yields, as shown in Table III. The nitrogen ligands are synthesized in fewer steps and are less expensive than phosphorous ligands such as DIOP. The highest reported ee for 1-phenylethanol in asymmetric hydrosilylation used ligand 7. One unusual feature of this ligand is that it was used as a 50:50 diastereomeric mixture in the reaction. No experimental evidence has been presented to explain this.

Scheme III



7 R=H, R'=Et
8 R=H, R'=Me
9 R=Me, R'=Me

10

11

12

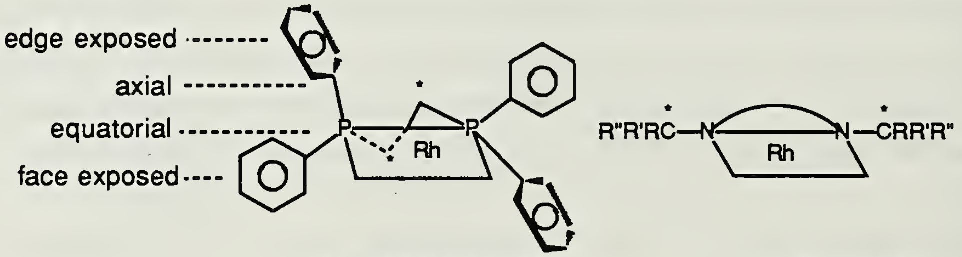
Table III. Hydrosilylation of Acetophenone with $[Rh(COD)Cl]_2$ and Ph_2SiH_2[a]

Ligand	Yield (%)	%ee	Configuration of product
7[20]	99	97	R
10[21]	91	94	S[b]
11[21]	c	91	R
8[20]	98	86	R
9[20]	90	84	R
12[11]	99	78	S

[a] Reaction conditions were not consistent. [b] $RhCl_3(H_2O)_3$ used instead. [c] Yield not reported.

To explain the high enantioselectivity of the nitrogen ligands over the phosphorous ligands, Brunner compared the their general structures, as shown in Scheme IV.[22] In the phosphorous ligands, the chirality of the alcohol is induced by the phenyl groups on the phosphorous atom. The two phenyl rings adopt an axial/equatorial and face/edge exposed conformation. Brunner asserts that the axial/equatorial configuration is due to the puckering of the chiral backbone of the ligand. This means the dissymmetry at the C* atoms is transmitted to the phosphorous phenyl groups, and then to the coordination site on the metal where the substrate is bound. Brunner claims that "loss of chiral information" occurs from the C* to the phosphorous, which gives low ee in the product. The face/edge exposure is due to the steric bulk of the two phenyl groups, and so they prefer to be perpendicular to each other. However, rhodium-DIOP complexes can be used to hydrogenate functionalized ketones in as high as 95% ee.[4b] If there is a loss of chiral information, then such high ee for any rhodium-DIOP complex should not be possible.

Scheme IV



phosphorous model

nitrogen model

In comparison, the chirality in the nitrogen ligands is located where the phenyl groups are in the phosphorous system. No loss of chiral information can occur, and the chiral C* can directly interact with the coordination site on the metal where the ligand is bound. Brunner contends that these complexes are highly enantioselective due to no loss in chiral information.

However, according to Brunner's theory, ligands with chiral phosphorous atoms bound directly to the metal atom, such as BMPP **4**, should give much higher ee than DIOP. However, as shown in Table II, the reverse is true.

Kagan attached (+)-DIOP to a synthetic achiral resin (Merrifield) to form a heterogeneous hydrosilylation catalyst.[18] The insoluble catalyst is easily separable by filtration at the end of the reaction, and is easily reused. The yield and ee are identical to the homogeneous version **1**, but a slight loss of rhodium from the resin was observed.

Silane

The identity of the silane can influence the ee as well as the configuration of the resulting silyl ether,[17] as shown in Table IV. Although it is unusual for the configuration to vary, the change in ee is common. No thorough testing of the different silanes has been tried to find a good general silane, but α-$NpPhSiH_2$ and Ph_2SiH_2 are used frequently. Also, no satisfactory explanations of the change in configuration and ee have been given.[23] A possible explanation is that the bulky siloxy group influences the conformation of the silyl ether in the asymmetric induction step.

Table IV. Hydrosilyation of ketones with $[BMPP]_2Rh(S)Cl^a$ and various silanes

Ligand	Ketone	Silane	Yield (%)	%ee	Config. of Product
(-)-(S)-BMPP	PhCOEt	$PhMe_2SiH$	96	50	R
"	"	Et_2SiH_2	98	17	S
"	$PhCO^iPr$	$PhMe_2SiH$	95	56	R
"	"	Et_2SiH_2	98	23	S
(+)-(R)-BMPP	$PhCO^cHex$	$PhMe_2SiH$	90	58	S
"	"	Et_2SiH_2	95	19	R

[a] S is solvent.

Ketone

Brunner varied the structure of the ketone while holding the reaction conditions constant to ascertain the effect on the ee on the products using his highly enantioselective ligand **7**.[24] The results are shown in Table V. If the ee is only dependent on the difference in steric bulk between R' and R", one would expect that large steric differences between R' and R" would give products with high ee, while small steric differences should give lower ee. Ketones **13** and **14** each have large steric differences, and the resulting alcohols are produced in higher ee than **16**, which has smaller steric differences. However, **15** would be expected to form the alcohol in higher ee. The isopropyl group in **18** would not be predicted to give such a low ee compared to the n-propyl in ketone **17**. Clearly, the ee is not only dependent on the steric bulk of the R' and R" groups on the ketone.

Table V. Hydrosilylation of various R'COR" with $[Rh(COD)Cl]_2$, Ph_2SiH_2 and ligand **7**.[a]

No.	R'	R"	Yield (%)	%ee
13	CH_3	Ph	90	84
14	CH_3	1-Naphthyl	95	81
15	CH_3	4-Phenylphenyl	90	60
16	Ph	2-Methylphenyl	70	15
17	Ph	n-Propyl	85	77
18	Ph	isopropyl	90	6

[a] Metal / ligand / siland / ketone ratio 1 / 8 / 16.5 / 15. All alcohols have the R configuration.

For alkyl ketones, the %ee and configuration of the product are related to the identity of R' and R", as shown in Table VI. As R' increases in length, the %ee's for both R"=CH_3 and R"=CH_2CH_3 drop. What is striking is the consistent difference in the configuration of the alcohols between R"=CH_3 and R"=CH_2CH_3. Brunner points out that the ee is dependent on the position of the carbonyl group along the alkyl chain, but does not suggest why.

Table VI. Hydrosilylation of various alkyl R'COR" with $[Rh(COD)Cl]_2$, Ph_2SiH_2 and ligand 7[a]

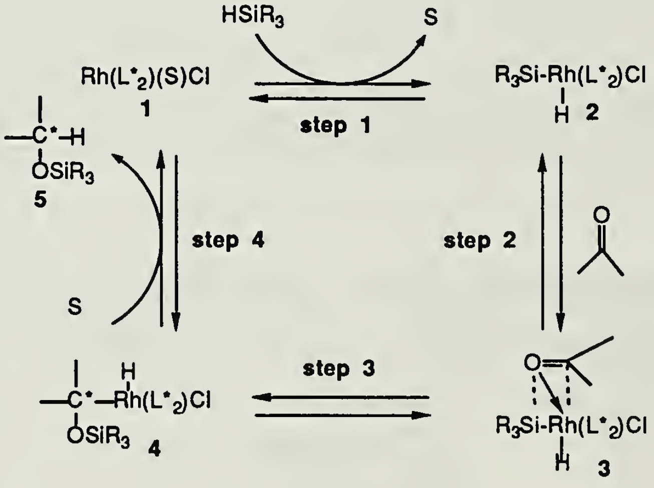
R'	R"=Me: Config.	Yield (%)	%ee	R"=Et: Config.	Yield (%)	%ee
n-Butyl	R	80	51	S	90	24
n-Pentyl	R	80	45	S	85	17
n-Hexyl	R	90	36	S	90	17
n-Heptyl	R	90	34	S	85	18

[a] Metal / ligand / siland / ketone ratio 1 / 8 / 16.5 / 15.

PROPOSED CATALYTIC CYCLE

Ojima proposes a catalytic cycle based on a detailed analysis of the steric course of the reaction,[25] and is shown in Scheme V. S is solvent. First, the silane is oxidatively added to a rhodium(I) complex to form **2**. The carbonyl of the ketone first binds in a dative manner to the rhodium to form **3**, and then inserts into the silicon-hydrogen bond to produce an α-siloxyalkylrhodium intermediate **4**. The silyl ether **5** is formed by reductive elimination of **4**.

Scheme V

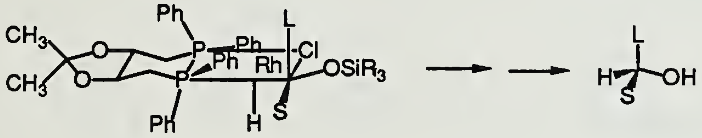


Some experimental evidence exists for this proposed catalytic cycle. Intermediate **2** has been found to precipitate from the achiral reaction.[5a] Evidence supporting intermediate **4** was found by Kagan while performing the hydrosilylation of acetophenone with diphenylsilane in the presence of a spin trap (nitrosodurene).[26] He detected PhMe(α-NpPhSiH-O-)C-N(O·)-Ar, where Ar=2,4,5,6-tetramethylphenyl), and concluded that the observed radical species was formed by addition of nitrosodurene with **4**. Kolb and Hetflejs analyzed the reaction by using a cationic rhodium-DIOP complex, and determined the rate determining step to be reduction of the ketone with the silyl(hydrido)rhodium(III) species, in other words, steps 2 and 3.[27] Their data was consistent with the proposed mechanism.

ASYMMETRIC INDUCTION STEP

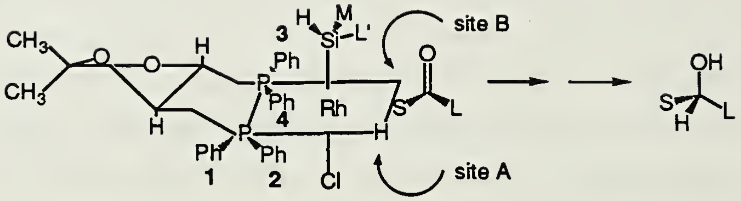
The step in the proposed catalytic cycle in which the configuration of the product is determined is not known. Two theories exist as to which is the asymmetry inducing step when the ligand is (+)-DIOP **1**. Ojima asserts that step 3 sets the configuration of the alcohol.[28] Intermediate **4** can be formed as diastereomers. Ojima predicts that the enantiomeric excess can be ascribed to product development control, with the most sterically preferable diastereomer formed determining the configuration of the major product. Ojima hypothesized what the most preferable conformation of intermediate **4** should be by examining Dreiding models. The result is shown in Scheme VI. A square-pyramidal structure for the rhodium was chosen by analyzing similar structures.[29] The ketone LCOS, where L=large and S=small groups, reacts to form the silyl ether in this conformation. The silyl group is considered to be larger than L. Ojima claims the model in Scheme VI does predict the correct configuration of the alcohol.

Scheme VI



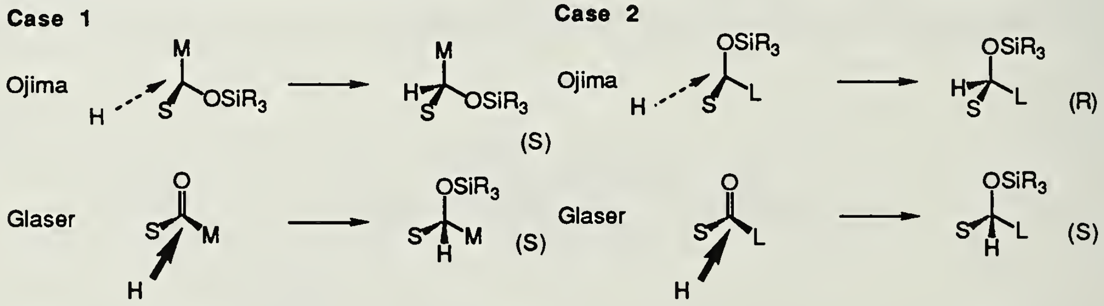
Glaser proposes that the configuration of the product is determined through steric approach control in step 2.[30] As the ketone approaches intermediate **2**, it has the choice between various diatereomeric faces in the complex. Most ketones will choose the most sterically favorable face, and produce enantiomerically enriched alcohol. Glaser hypothesized what the most sterically preferred conformation of **2** should be using CPK space-filling models. This is shown in Scheme VII. The ketone prefers to coordinate to site B on the intermediate to avoid steric interaction with phenyl group **1** at site A. The large group L on the ketone will prefer to point away from the phenyl groups **3** and **4**. Glaser claims this model also correctly predicts the correct configuration of the alcohol with few exceptions.

Scheme VII



One way to differentiate these two theories is to see whether they agree with experimental evidence. If the ketone and hydride are kept in the same configurations and the rest of the atoms are removed in each model, the simplified models look like those shown in Scheme VIII. L is the large group, M is medium, and S is small, with order of precedence L>M>S. If the siloxy group is bulkier than L or S, as in Case 1, both models predict the same configuration of the product. However, if L is bulkier than the siloxy group, opposite configurations are predicted, as in Case 2. In Glaser's model, the silane plays no role in determining the configuration or ee of the product, unlike Ojima's model. Experimental evidence shows that the silane can influence the configuration of the product and the ee, which lends support to Ojima's model. In Glaser's studies, the silane used was α-NpPhSiH$_2$, so all his runs go by Case 1, which is why he obtains the correct configurations.

Scheme VIII



Ojima's model also suggests that the configuration of the alcohol cannot be predicted just from the difference in bulk of L and S, but that the bulkiness of the siloxy group must also be taken into account. The data in Tables V and VI support this idea.

Although the asymmetric hydrosilylation of acetophenone proceeds in high ee, few other chiral alcohols can be produced by this method. There is a lack of a general, highly enantioselective hydrosilylation method applicable to a variety of ketones. Consequently, this reaction is not yet synthetically useful.

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MECHANISTIC STUDIES OF THE HYDROLYSIS OF PROSTACYCLIN

Reported by Martha Burnett April 20, 1990

INTRODUCTION

In 1976, Vane[1] and Needleman[2] independently observed the conversion of arachidonic acid to a labile compound which had pronounced anti-coagulative properties. The characterization of this new compound was carried out mainly by mass spectral studies and by considering the probable biosynthetic pathways.[3] These studies indicated that this compound had structure 1, lacking only the configuration of the 5,6 double bond. This structure was confirmed and the stereochemistry defined by total synthesis.[4]

Prostacyclin has a wide array of biological activities. It is the most potent anticoagulant known. It also is a vasodilator, a weak bronchodilator, and a cytoprotective agent in both myocardial tissue and in the stomach. It also has been shown to lower blood pressure, probably in conjunction with the relaxation of vascular tissue.[5]

The high level of anticoagulant activity of prostacyclin has made it an attractive target as a medicinal treatment for thrombosis, but prostacyclin's extremely short half-life at physiological pH ($t_{1/2}$=3.5 min at pH=7.48)[6] limits its pharmaceutical usefulness. The possibility of new drug development has led to mechanistic studies of the hydrolysis of prostacyclin and to the synthesis of many stable analogs. In this seminar, I will be presenting some recent studies of the mechanism of hydrolysis of prostacyclin (1).

BACKGROUND

In 1976, it was shown that the product of hydrolysis of prostacyclin is 2 (Scheme I).[6] This indicates that the mechanism involved in the breakdown of prostacyclin is acid catalyzed hydrolysis of vinyl ethers. This reaction has been extensively studied. It is generally believed to follow the mechanism shown in Scheme II.[7] Studies have shown that several structural modifications have effects on the rate of the reaction. For example, it was known that cis double bonds hydrolyze faster than trans by up to a factor of 5,[8] that phenyl substitution at the beta position stabilizes the compound toward hydrolysis,[7] and that exocyclic double bonds are more reactive than endocyclic double bonds.[9] In the course of these investigations, the rate constants for 3 and 4 (which to a first approximation mimicked the structure of prostacyclin) were found to be 635 M^{-1} s^{-1} and 314 M^{-1} s^{-1} respectively.[10] The rate constant found for prostacyclin is 37000 M^{-1} s^{-1}.[6]

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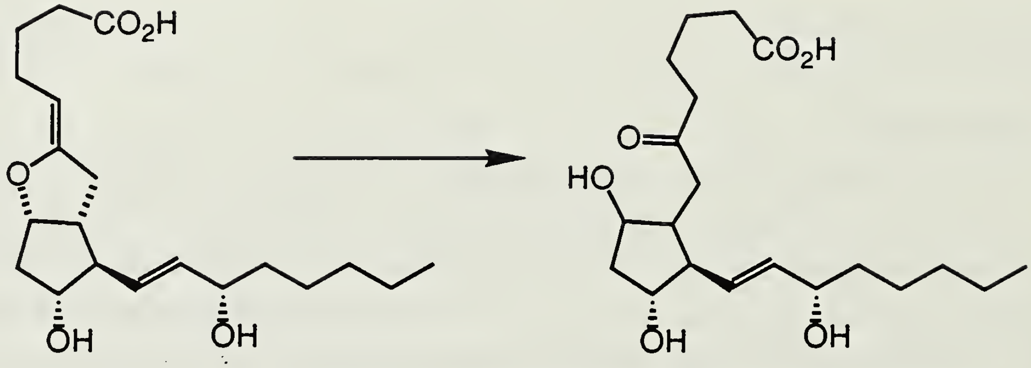
Scheme I



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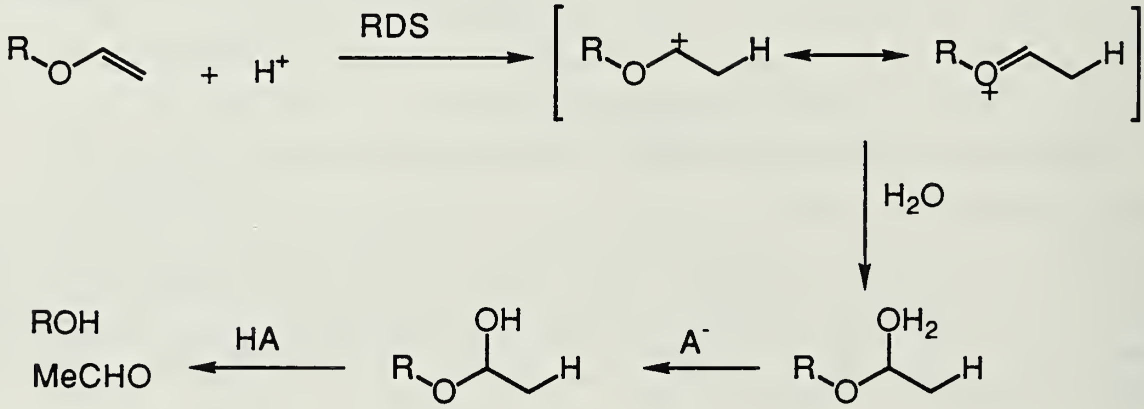
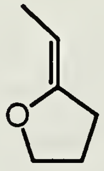
Scheme II





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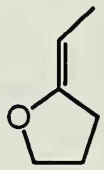

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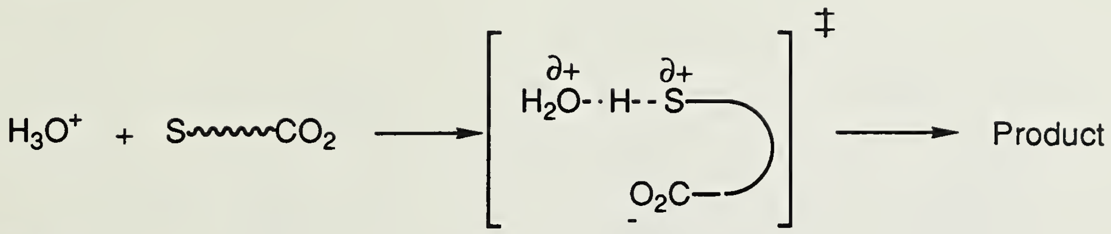
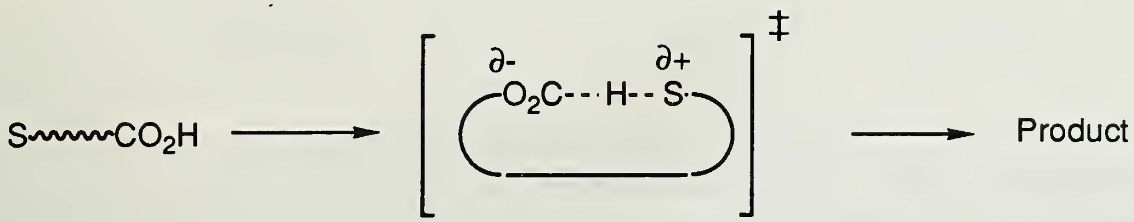
MECHANISTIC STUDIES

Several proposals have been made to explain the unusual lability of prostacyclin. The earliest involved the release of ring strain of the cis fused five-membered ring system.[6] Two later proposals involved the carboxylate form of prostacyclin. In one, the carboxylic anion stabilizes the positive charge developing in the transition state via an electrostatic field effect (Scheme III). The other involves a rapid equilibrium to the acid followed by a general acid catalysis (Scheme IV).[11]

Scheme III



Scheme IV

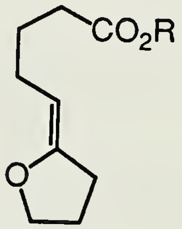


While the first proposal is easily distinguished from the second pair, differentiating between the latter is difficult because they are kinetically identical.

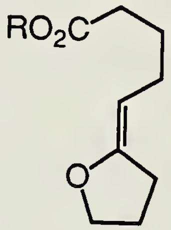
Kinetic studies of several compounds have been used to address the issue of the extra reactivity of the prostacyclin system. The rate measurements were performed in dilute $HClO_4$, dilute HCl, and in a variety of buffers. Using DCl, D_2O, and DOAc, values for k_H/k_D and k_{HOAc}/k_{DOAc} were obtained. The rate of reaction was followed by monitoring the change in absorbance of the vinyl ether group at approximately 210 nm.

In 1986, Kresge reported a complete kinetic profile of prostacyclin.[11] One of the most intriguing discoveries was that the curve showing the dependence of the observed rate on $[H^+]$ consists of two distinct linear portions. Since the transition between the two linear portions occurs at the approximate pH of a carboxylic acid of this type, Kresge proposed that the acid and the carboxylate hydrolyze at different rates. This led to the proposals of electrostatic and general acid catalysis mentioned earlier in this paper. It also spoke against the strain hypothesis since the carboxylic acid and the carboxylate should be equally strained. A second observation made in this study was that undisassociated acid catalyzes the hydrolysis of the methyl ester of prostacyclin (which has a rate constant typical of vinyl ethers) but has little or no effect on the hydrolysis of prostacyclin itself. The k_H/k_D values agreed more closely with what was predicted for general acid catalysis than for electrostatic stabilization.

In 1987, Bergman and Kresge[12] reported that model compound 5 shows a similar kinetic profile to that of prostacyclin. The methyl ester of this compound also shows similar behavior.



5a R = H
5b R = Me



6a R = H
6b R = Me

This is strong evidence against the strain hypothesis, as compound 5a does not contain the strained bicyclic [3.3.0] ring system, and hydrolyzes 1.7 times faster than prostacyclin itself. This acceleration can be rationalized using the general acid catalysis mechanism. In this proposal, the carboxylate function must approach the double bond in a plane perpendicular to it. In the cis fused system, one side is blocked whereas in the model compound both sides are easily accessible.

Bergman next turned to compounds 6a and 6b.[13] He again found a very similar rate profile. The overall rate of compound 6 differs from compound 5 by a factor of 3 with the cis isomer hydrolyzing faster, as is expected for vinyl ethers. The fact that the E and Z isomers have similar rate profiles raises an interesting point. According to Scheme I, the positive charge is mainly building up on the oxygen. In the E isomer, it would be geometrically difficult for the carboxylate anion to get to a position coplaner with the double bond and yet close to the oxygen. Both of these requirements are necessary if the negative carboxylate is to stabilize the positive charge in the transition state. If the electrostatic mechanism were in operation, one would expect a large difference in rate due to the geometry of the system. The same restraint would not be present for the general acid catalysis because in this mechanism the carboxylate approaches in a plane perpendicular to the double bond.

Compound 7a was known to be a stable analog of prostacyclin.[14] It was initially thought to be stabilized solely by the conjugation of the phenyl ring with the vinyl ether. It was found through studies on 7a and b,[15] 8a and b, and 9a and b,[16] that, in these compounds, the rate of hydrolysis of the ionized forms is not much faster than that of the unionized form.

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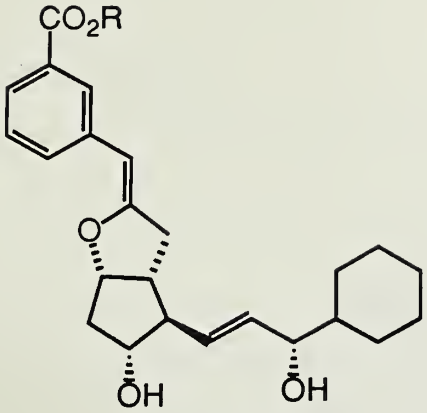
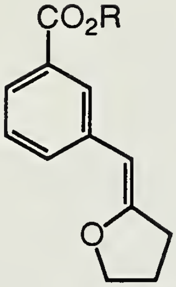
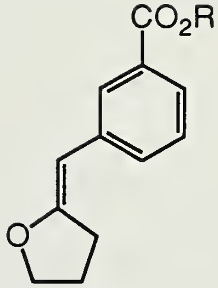


7a R = H
7b R = Me



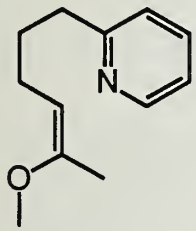
8a R = H
8b R = Me



9a R = H
9b R = Me

The small increase that was observed could be easily explained by the negative charge of the carboxylate attracting the proton . The acid form of 7a has a 89-fold decrease in reactivity relative to prostacyclin. This can be attributed to the conjugation effects. Examination of the ionized form showed a decrease of 3350-fold compared to the carboxylate form of prostacyclin. This extra stability can be attributed to lack of intramolecular catalysis due to the rigidity of the phenyl ring.

Most recently, Bergman has reported kinetic studies done on compounds 10 - 12 in which a pyridine ring replaces the carboxylic acid group.[17]



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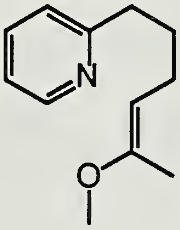

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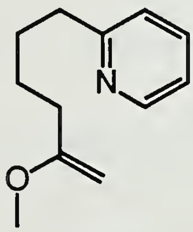

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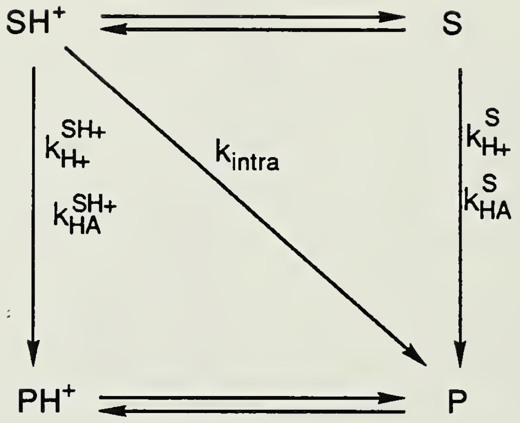
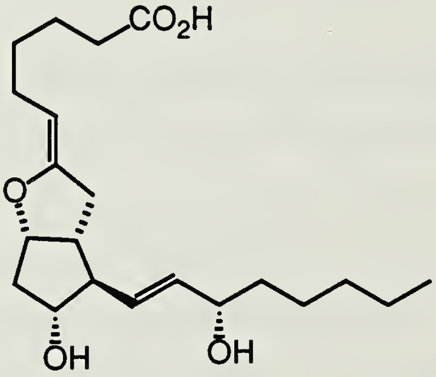
This eliminates the possibility of catalysis by electrostatic stabilization because the pyridine ring never develops a negative charge. In these studies, he found a rate acceleration of k_{H^+}'/k_{H^+} equal to 45.7 compared to 99 for that of prostacyclin. He also found that 87%-95% of the reaction proceeds through intramolecular catalysis (defined as the pyridinium form of the substrate going directly to the pyridine form of the product - Scheme V).

Scheme V



This intramolecular scheme is what one would expect for intramolecular general acid catalysis. Bergman also reported that structure 9 has a k_{H^+}'/k_{H^+} equal to 15.7. This can be compared to a k_{H^+}'/k_{H^+} equal to 8 for homoprostacyclin (structure 13).[18]



13

This large difference in catalytic efficiency can be attributed to the difference in ring size in the transition state of catalysis.

CONCLUSIONS

In the past several years there has been much research done involving prostacyclin. One of the areas of interest has been its mechanism of hydrolysis. One of the major ways of studying this question is by studying the kinetics of the reaction. These recent kinetic studies point to an intramolecular general acid catalysis as the cause of the acceleration of the reaction.

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